

**DIETARY SUPPLEMENTATION WITH EICOSAPENTAENOIC ACID  
IN PATIENTS WITH SCHIZOPHRENIA:  
NEUROPSYCHOLOGICAL EVALUATION OF COGNITIVE FUNCTIONING**

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(Clinical Psychology) at the University of Stellenbosch**

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## **DECLARATION**

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and has not previously, in its entirety or in part, been submitted at any university for a degree.

Henda Dippenaar

## SUMMARY

Schizophrenia is known to produce positive (e.g. hallucinations) and negative symptoms (e.g. social withdrawal). Cognitive dysfunction has long been recognised as common in schizophrenia and is now accepted as a third cardinal feature, thought strongly to be associated with negative symptoms. While positive symptoms may respond well to antipsychotic medication, the negative symptoms have typically been resistant to all forms of intervention. A current study looking at the efficacy of Eicosapentaenoic Acid (EPA), indicated a potential for negative symptoms to improve, although not significantly ( $P=0.14$ ). The purpose of this research was to expand the above mentioned study, by evaluating the potential of EPA for improving cognitive function in patients with schizophrenia.

Forty patients diagnosed with schizophrenia were randomly ascribed to one of two groups in a 12 week, double-blind, placebo-controlled study. The following neuropsychological tests were administered to patients at baseline and end point: Mini Mental State Examination (MMSE); Rey Auditory-Verbal Learning Test (RAVLT); Visual Reproduction, Wechsler Memory Scale - Revised (VR, WMS-R); Rey-Osterreith Complex Figure Test (ROCF); Trail Making Tests (TMT-A; TMT-B); Controlled Oral Word Association Test (COWAT); Similarities, South African Wechsler Adult Intelligence Scale - Revised (Similarities, SAWAIS-R); Boston Naming Test (BNT).

There were no overall significant differences in neuropsychological function between the experimental (EPA) and the control (Placebo) group. In some isolated tests the experimental group did significantly better than the control group, but for other tests the control group did significantly better than the experimental group. Large intragroup variation - particularly within the EPA group - was indicated. In the EPA group only one out of 25 independent neuropsychological test scores showed a significant correlation with the symptom severity on the Positive and Negative Syndrome Scale (PANSS) total score (% change). There were no significant correlations between any of the neuropsychological test scores in the EPA group and on the dyskinesia subscore of the Extrapyrimal Symptom Rating Scale (ESRS).

There was no evidence to support the hypothesis that EPA improved cognitive functioning in patients with schizophrenia.



## OPSOMMING

Dit is bekend dat skisofrenie positiewe (bv. hallusinasies) en negatiewe simptome (bv. sosiale onttrekking) voortbring. Kognitiewe disfunksie word lank reeds beskou as algemeen in skisofrenie en word nou aanvaar as 'n derde kardinale eienskap wat sterk geassosieer word met negatiewe simptome. Terwyl positiewe simptome goed reageer op antipsigotiese medikasie, is die negatiewe simptome tipies meer weerstandig teen all vorme van intervensie. 'n Huidige studie wat die effektiwiteit van *Eicosapentaenoic Acid* (EPA) ondersoek, het 'n potensiaal vir die verbetering in negatiewe simptome aangedui, alhoewel nie beduidend nie ( $P=0.14$ ). Die doel van hierdie navorsing was om bogenoemde studie uit te brei, deur te evalueer wat die potensiaal van EPA is om kognitiewe simptome in pasiënte met skisofrenie te verbeter.

Veertig pasiënte gediagnoseer met skisofrenie is ewekansig toegewys aan een van twee groepe in 'n 12 weke, dubbel-blinde, plasebo-gekontroleerde studie. Die volgende neurosielkundige toetse is afgeneem op pasiënte by basislyn en eindpunt: *Mini Mental State Examination* (MMSE); *Rey Auditory-Verbal Learning Test* (RAVLT); *Visual Reproduction, Wechsler Memory Scale - Revised* (VR, WMS-R); *Rey-Osterreith Complex Figure Test* (ROCF); *Trail Making Tests* (TMT-A; TMT-B); *Controlled Oral Word Association Test* (COWAT); *Similarities, South African Wechsler Adult Intelligence Scale - Revised* (Similarities, SAWAIS-R); *Boston Naming Test* (BNT).

Daar was geen beduidende verskille in neurosielkundige funksionering tussen die eksperimentele (EPA) en kontrole (Plasebo) groep nie. In 'n paar geïsoleerde toetse het die eksperimentele groep beduidend beter as die kontrolegroep gevaar, maar op ander toetse het die kontrolegroep beduidend beter as die eksperimentele groep gevaar. Groot intragroep variansie - in veral die EPA groep is aangetref. In die EPA groep het slegs een uit die 25 onafhanklike neurosielkundige toetstellings gedui op 'n beduidende korrelasie met die erns van simptome op die *Positive and Negative Syndrome Scale* (PANSS) totale telling (% verandering). Daar was geen beduidende korrelasie tussen enige van die neurosielkundige toetstellings in die EPA groep en op die diskinesie-subtelling op die *Extrapyramidal Symptom Rating Scale* (ESRS) nie.

Daar was geen bewyse om die hipotese te steun dat EPA kognitiewe funksionering in pasiënte met skisofrenie verbeter nie.



The article format of this thesis is in accordance with the requirements of the Department of Psychology.

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<b>CONTENTS</b>	<b>PAGE</b>
<b>Title Page</b>	1
<b>Abstract</b>	2
<b>1. Introduction</b>	3
<b>2. Methods</b>	6
<i>2.1. Subjects</i>	6
<i>2.2. Procedure and design</i>	6
<i>2.3. Cognitive assessment</i>	8
<i>2.4. Data analysis</i>	9
<b>3. Results</b>	11
<i>3.1. Neuropsychological change from baseline to end point</i>	11
<i>3.2. Composite neuropsychological test scores</i>	13
<i>3.3. Correlations among neuropsychological tests and symptom improvement</i>	13
<b>4. Discussion</b>	16
<b>References</b>	19
<b>List of Tables</b>	
Table 1: Descriptive statistics for the 40 patients with schizophrenia at baseline	7
Table 2: Mean change scores and significance of change between baseline and end point values for each patient group	11
Table 3: Comparisons of mean change scores and significance among patients receiving EPA and patients receiving Placebo	12
Table 4: Composite scores of neuropsychological tests for each patient group	13
Table 5: Spearman correlations among symptom severity (total PANSS score); dyskinesia movements (subscale of ESRS) and neuropsychological tests for each patient group	14



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**Abstract**

*Introduction and study objectives:* Schizophrenia is known to produce positive (e.g. hallucinations) and negative symptoms (e.g. social withdrawal). Cognitive dysfunction has long been recognised as common in schizophrenia and is now accepted as a third cardinal feature, thought strongly to be associated with negative symptoms. While positive symptoms may respond well to antipsychotic medication, the negative symptoms have typically been resistant to all forms of intervention. A current study looking at the efficacy of Eicosapentaenoic Acid (EPA), indicated a potential for negative symptoms to improve, although not significantly ( $P=0.14$ ). The purpose of this research was to expand the above mentioned study, by evaluating the potential of EPA for improving cognitive function in patients with schizophrenia.

*Subject and methods:* Forty patients diagnosed with schizophrenia were randomly ascribed to one of two groups in a 12 week, double-blind, placebo-controlled study. The following neuropsychological tests were administered to patients at baseline and end point: Mini Mental State Examination (MMSE); Rey Auditory-Verbal Learning Test (RAVLT); Visual Reproduction, Wechsler Memory Scale - Revised (VR, WMS-R); Rey-Osterreith Complex Figure Test (ROCFT); Trail Making Tests (TMT-A; TMT-B); Controlled Oral Word Association Test (COWAT); Similarities, South African Wechsler Adult Intelligence Scale - Revised (Similarities, SAWAIS-R); Boston Naming Test (BNT).

*Results:* There were no overall significant differences in neuropsychological function between the experimental (EPA) and the control (Placebo) group. In some isolated tests the experimental group did significantly better than the control group, but for other tests the control group did significantly better than the experimental group. Large intragroup variation – particularly within the EPA group - was indicated. In the EPA group only one out of 25 independent neuropsychological test scores showed a significant correlation with the symptom severity on the Positive and Negative Syndrome Scale (PANSS) total score (% change). There were no significant correlations between any of the neuropsychological test scores in the EPA group and on the dyskinesia subscore of the Extrapyramidal Symptom Rating Scale (ESRS).

*Conclusions:* There was no evidence to support the hypothesis that EPA improved cognitive functioning in patients with schizophrenia.

*Keywords:* Schizophrenia; Neuropsychological assessment; Cognitive functioning, Eicosapentaenoic Acid.



## 1. Introduction

Traditionally schizophrenia has been viewed as an illness comprised primarily of positive (e.g. hallucinations and delusions) and negative symptoms (e.g. affective flattening, alogia, avolition, social withdrawal). The presence of positive symptoms can bring about cognitive dysfunction (e.g. poor insight and judgment, lack of concentration and working memory deficits) (Berman et al., 1997; Keefe, 2000). However, it is accepted that there can be primary and pervasive cognitive deficits that are independent of positive symptoms in that they persist after the resolution of the positive psychotic symptoms (Addington, 2000; Sharma, 1999).

Many studies found that negative symptoms may be associated more consistently with cognitive deficits (Berman et al., 1997; Hoff, 1995; Keefe, 2000; Palmer et al., 1997) and change in cognitive performance (Gold et al., 1999). Other studies have indicated associations of isolated cognitive functions with positive symptoms (Berman et al., 1997; Keefe, 2000). However, in a recent review of studies ranging from 1958 to 1999, Addington (2000) presented evidence to suggest that cognitive impairment is a distinct construct that has shown to be more stable than – although related to – negative symptoms. Negative symptoms only seem to account for a small proportion (~10%) of the variance in cognitive impairment and this may account for the overall lack of consistency of results. Green and Nuechterlein (1999) added that neurocognitive deficits appear to start earlier than negative symptoms and that it is entirely possible that the critical pathway runs from neurocognitive deficits to negative symptoms. It is now acknowledged that cognitive impairment is the third key symptom in schizophrenia (Breier, 1999).

Cognitive dysfunction has long been recognised as a cardinal feature of schizophrenia, dating back to Krapelin's description of *dementia praecox* (1919). Despite a vast literature, the exact timing and course of the neuropsychological/cognitive deficits remains obscure. Weickert and Goldberg (2000) conclude that the cognitive deficits associated with schizophrenia may emerge along three developmental trajectories based on the degree and timing of impairment of general intellect. One course suggests that cognitive impairment may be relatively profound and widespread at an early stage of development causing premorbid intellectual and cognitive deficits, and remains present subsequent to the onset of psychotic symptoms. The neurodevelopmental theory of schizophrenia hypothesises the existence of a "schizophrenic brain lesion" which remains largely dormant until further brain maturation calls the damaged neuronal systems into operation (Lishman, 1998). Yet another course may be that the cognitive deficits may manifest concurrently with the onset of psychotic symptoms, resulting in a more circumscribed pattern of deficits that encompasses the



cognitive domains of executive function, attention and long-term memory. The third course suggests that while cognitive impairment may be concurrent with symptom onset, the debilitating cognitive deficits associated with the disease process may be relatively subtle.

A fourth theory could be that first onset patients presenting with schizophrenia are still cognitively intact, but would follow a neurodegenerative process as the illness continues. However, no published evidence was found to support this view (Rund, 1998). Rather, evidence implies that there is no cognitive deterioration over the course of living with schizophrenia (Addington, 2000; Harvey et al., 1995; Hoff, 1995). This is consistent with a previous review of 15 longitudinal studies of cognitive dysfunction in schizophrenia patients, in which Rund (1998) concludes that after the onset of schizophrenia cognitive deficits are relatively stable over long periods. Most evidence supports findings of either no change (Hoff, 1995) or an improvement in cognition over the course of the illness (Gold et al., 1999; Hoff et al., 1999).

Early cognitive and negative symptoms are predictive of poor functional outcome (Birchwood, 1999; Sharma, 1999; Weickert and Goldberg, 2000). These would include a variety of domains involved with the acquisition and retention of skills needed for social, vocational and community functioning (Breier, 1999; Green et al., 2000; Mueser, 2000). It is now recognised that functional deficits in schizophrenia are responsible for much of the disability and indirect cost of illness. Cognitive impairment has been strongly associated with impaired social perception, social skill, social functioning, the course of illness and response to psychosocial treatment (Mueser, 2000). Conversely, cognitive improvement has been linked with good outcome status and quality of life (Green, 1996; Silverstein et al., 1997).

Studies have also explored the effect of neuroleptic medication on outcome and specifically the relationship between antipsychotic drugs and cognition. However, conclusions remain elusive and studies contradict each other. Antipsychotic medication (neuroleptics) is documented both to worsen (Green and Nuechterlein, 1999; Keefe et al., 1999) and to improve (Sharma, 1999; Keefe et al., 1999; Keefe, 2000) aspects of memory. In general, neuroleptics are thought to have little effect on cognition in schizophrenic patients (Blyler and Gold, 2000) and the therapeutic benefits are predominantly limited to the positive symptoms of the illness. These drugs have substantially less impact on negative symptoms, mood symptoms and cognitive impairment (Keefe et al., 1999). Therefore most patients improve with medication as psychotic symptoms decrease, but they struggle with lingering cognitive deficits (Sharma, 1999). Some studies show atypical antipsychotic



drugs to reduce cognitive impairment associated with schizophrenia (Goldberg et al., 1993; McGurk, 1999), but again studies have shown inconsistent findings.

The pathophysiology of schizophrenia was previously mainly explained by the dopamine hypothesis. There is now substantial evidence that abnormal phospholipid and related fatty acid metabolism may contribute to schizophrenia (Horrobin and Bennett, 1999). In the cerebral cortex of patients with schizophrenia, there is evidence of an increased rate of phospholipid breakdown such as might be produced by increased phospholipase A2 (PLA2) activity (Horrobin, 1996). The replacement of highly unsaturated fatty acids (HUFAs) back into the membrane is too slow, which results in damaged membranes. The membrane phospholipid hypothesis thus leads to the prediction that treatment with PLA2 inhibitors should result in clinical improvement in schizophrenia. A natural inhibitor of PLA2 is eicosapentaenoic acid (EPA), an omega-3 HUFA abundantly present in sardine oil, which may potentially be used to restore the structure and function of the damaged membranes. Christensen and Christensen (1988) suggested that dietary lipid intake might be important in the outcome of schizophrenia. Mellor et al. (1995) found that the omega-3 essential fatty acids and particularly EPA contributed significantly to the variance in schizophrenic symptoms. In a recent single patient study (Puri and Richardson, 1998), it was shown that an emulsion providing two gram EPA per day, improved both positive and negative symptoms in a drug-naïve patient. A search on *Medline* and *PsychLit* rendered no reports that assessed the effect of EPA on cognitive functioning in patients with schizophrenia.

Literature on the neuropsychology of schizophrenia has been controversial regarding both the existence and proper characterisation of cognitive impairment (Binks and Gold, 1998). This is exacerbated by findings of significant individual variability in the overall severity of cognitive deficits in patients with schizophrenia (Laws and Kondel, 1998). It raises the controversial issue of which neuropsychological tests to use in the assessment of these cognitive deficits. The cognitive deficits that are most reported in literature relate to the areas of attention, memory, executive function and communication (Sharma, 1999). However, a wide variety of cognitive areas have been assessed and vary widely between studies (Keefe et al., 1999), and as yet no validated neurocognitive battery exists for the schizophrenic population (Velligan and Miller, 1999).

It is important to assess cognitive function as an outcome measure because of its strong associations with negative symptoms and quality of life in schizophrenia (Green, 1996). The purpose of this study was to evaluate the potential of EPA to improve cognitive functioning in



patients with schizophrenia. Neuropsychological tests were used as efficacy parameters. The study was part of a larger study evaluating the potential antipsychotic effect of EPA in schizophrenia.

## 2. Method

### 2.1 Subjects

Forty patients meeting DSM-IV (American Psychiatric Association - Fourth Edition 1994) criteria for schizophrenia were recruited from Stikland Hospital, Cape Town, South Africa, and surrounding clinics. A Senior Psychiatry Registrar confirmed the patients' diagnoses by direct interview and reviewing hospital records. Inclusion criteria for this study were a minimum total score on the Positive and Negative Syndrome Scale (PANSS) of >60. Additionally, patients had to have been on a stabilised medication regime for at least six months. Written, informed consent from either the subject or the legal guardian was obtained prior to taking part in the study. Exclusion criteria were substance abuse, neurological disorder and other significant medical conditions.

Of the 40 original patients, one was lost to follow up and unable to complete the study. The final sample consisted of 39 subjects with 19 subjects in the eicosapentaenoic acid (EPA) group and 20 in the control (placebo) group. There was no significant difference between the two groups for gender. The gender distribution within the two groups were as follows: in the EPA group 8 (40%) were female and 12 (60%) male, and in the control (placebo) group 7 (35%) were female and 13 (65%) male. The mean age of the subjects at baseline in the EPA group was 46.2 years (SD = 10.62; range = 29.09/61.04) and in the control (placebo) group 43.6 years (SD = 13.87; range = 17.10/69.12). The mean duration of illness before baseline was 22.65 years (SD = 10.5) with no significant difference between the two groups ( $P = 0.79$ ). The mean educational level of participants was 9.35 years (SD = 2.46) of education with no significant difference between the two groups ( $P = 0.90$ ). All patients were treated with neuroleptic medication during the study and were on a stabilized medication regime for at least six months prior to the study. The average dosage of chlorpromazine equivalent was 971.30 mg per day (SD = 589.24) with no significant difference between the two groups ( $P = 0.67$ ). The average dietary intake of EPA per week was 51.72 mg (SD = 53.61) with no significant difference between the two groups ( $P = 0.77$ ). The PANSS total score at baseline indicates no significant difference between the two groups ( $P = 0.62$ ). Table 1 summarizes characteristics of the sample. The two groups were highly comparable in most aspects, with no significant differences on any of the variables.



## 2.2. Procedure and Design

At baseline the first author, a Clinical Psychologist Intern, administered the neuropsychological tests in the following sequence: Mini Mental State Examination (MMSE) (Folstein et al., 1975); Rey Auditory-Verbal Learning Test (RAVLT) (Rey, 1964); Visual Reproduction, Wechsler Memory Scale - Revised (VR WMS-R) (Wechsler, 1987); Rey-Osterrieth Complex Figure Test (ROCF) (Rey, 1941; Osterrieth, 1944); Trail Making Tests (TMT) (Army Individual Test Battery, 1944); Controlled Oral Word Association Test (COWAT) (Spren and Benton, 1977); Similarities, South African Wechsler Adult Intelligence Scale - Revised (Similarities SAWAIS-R) (Wechsler, 1981) and the Boston Naming Test (BNT) (Kaplan et al., 1983).

Table 1

Descriptive statistics for the 40 patients with schizophrenia at baseline

Variable	Patients Given EPA (n=20)	Patients Given Placebo (n=20)
Gender		
Male	12 60%	13 65%
Female	8 40%	7 35%
Age at baseline (years)	46.2 (10.62) [29.9-61.4]	43.6 (13.87) [17.10-69.12]
Duration of illness (years)	23.1 (8.52)	22.2 (12.37)
Education (years)	9.4 (4.50) [3-14]	9.3 (2.27) [3-12]
Chlorpromazine equivalent (mg/day)	1011.4 (532.03)	931.2 (652.87)
EPA dietary intake (mg/week)	55.5 (54.79)	47.9 (53.55)
PANSS (total score)	67 (12.70)	74 (15.30)
% Compliance	97.8 (3.11)	97.8 (3.14)

Values are mean (SD) [range]

In addition, the following rating scales were administered by a Senior Psychiatry Registrar: Positive and Negative Symptom Scale (PANSS) and the dyskinesia subscale of the Extrapyramidal Symptom Rating Scale (ESRS). A Registered Dietitian calculated patients' dietary intake of EPA by evaluating hospital eating plans and consulting caregivers of those patients from the surrounding clinics.

Thereafter patients were randomly assigned to one of two treatment arms for 12 weeks of double-blind treatment. Group A received their standard antipsychotic medication plus an encapsulated EPA supplement, (Laxdale Ltd.) 3mg per day, i.e. 6 capsules twice daily. There are no known side effects of the oil supplement and it has been granted the Food and Drugs Administration (FDA) designation "Generally Regarded as Safe" (Crone et al., 2001). Group B received their standard antipsychotic medication plus a placebo. Patients had no change in their antipsychotic medication type or dose for the 12 week duration of the study.

After 12 weeks of double-blind treatment the neuropsychological assessment was repeated, in addition to the rating scales mentioned above.

### *2.3. Cognitive Assessment*

The Mini Mental State Examination (MMSE), probably the most widely used brief screening instrument for dementia (Lezak, 1995), was applied as described in Lezak (1995) and used as a measure for global cognitive functioning. The standardised administration and scoring procedures were followed. In addition, orientation scores were evaluated separately (Demakis et al., 2000).

The Rey Auditory-Verbal Learning Test (RAVLT) is a measure of verbal learning and memory and was administered as described in Lezak (1995). Scores were obtained for each of the five successive presentations, an interference trial (Trial B); a post interference free recall of the words from the original list (Trial VI), a 30 minute interval delayed recall (Trial VII) and a delayed recognition trial in which an adjusted score was calculated by subtracting the total false positives from the total true positives score. Repetitions, errors, new words learned, total words, percentage retention after the interference task and with delay, were also calculated (Lezak, 1995).

Visual Reproduction (Immediate VRI and Delayed recall VR II), is a subtest of the WMS-R and assesses visual memory. Each design was administered and scored in accordance with the WMS-R manual (Wechsler, 1987).

The Complex Figure Organisational Quality Scoring system developed by Hamby et al. (1993) gives an indication of organisational quality. The Rey-Osterreith Complex Figure Test (ROCFT) was used as a measure of constructional ability and visual perceptual organisation and it was administered according to Lezak (1995).

The Trail Making Test (TMT) is an integrative cognitive efficiency measure involving visual motoric coordination and integration, vigilance, attention, concentration and mental flexibility (Gard et al., 1999; Lezak, 1995) and was also administered according to Lezak (1995). Only the time taken to complete the trials was scored.

The Controlled Oral Word Association Test (COWAT) measures verbal fluency and executive initiation. Patients were asked orally to generate as many words as they could, beginning with the given letter (English: FAS, Afrikaans: VAS) of the alphabet. The sum of the scores on each letter is



the total raw score (Lezak, 1995; Mitrushina et al., 1999). This test was administered in the patient's home language.

Similarities, test 5 of the SAWAIS-R (Wechsler, 1987), is a test of abstract reasoning and verbal concept formation where the patient must explain what each of a pair of words has in common. It was administered in accordance with directions in the SAWAIS-R test booklet and scored by using the 'Guide to Marking' in evaluating responses. Standardised English and Afrikaans versions were available.

The Boston Naming Test (BNT) involves visual object confrontation naming and was administered and scored according to Lea and Febiger (Kaplan et al., 1983). Patients were presented with drawings of items and instructed to give the common name for each. This graded naming test gives an indication of vocabulary level and ease and accuracy of word retrieval (Lezak, 1995). The total score on this test is the number of correct responses produced spontaneously without the aid of a cue. Confrontation naming ability is mainly affected by educational level, but also age and culturally determined linguistic background and accumulated vocabulary (Mitrushina et al., 1999). The BNT is not standardised for the South African population as it contains items not commonly used, e.g. 'pretzel' and 'beaver'. No Afrikaans version is available and translation affects ascending difficulty. Afrikaans home language patients were asked to do this test in Afrikaans and were used as their own controls in the retest at end point.

#### *2.4. Data analysis*

The aim of this study was to determine change in cognitive functioning from baseline to study termination. A significant statistical level of  $P < 0.05$  was used throughout. The Kolmogorov-Smirnov was used to test deviations from normality and parametric and non-parametric statistical methods were employed accordingly. The Mann-Whitney  $U$  test compared groups depending on departures from normality. All other comparisons of continuous variables were evaluated with independent  $t$ -tests.

The EPA and placebo group were matched groups, and were determined by calculating demographic differences between groups in gender, age, duration of illness, education, chlorpromazine equivalent intake, EPA dietary intake, total PANSS score at baseline and percentage compliance.



The t-test for dependent samples was computed to compare the means for test results at baseline and at study termination. Practice effect was taken into account by both groups being demographically matched and being equally assessed with matched test instruments and matched time intervals. This was done by subtracting the baseline value from the end point value in each group and then comparing this new value between the experimental group and control group with the t-test for independent samples. Statistical computations were done for raw scores, as appropriate normative data could not be identified for most tests used. Effect size was calculated by subtracting end point from baseline mean, divided by the average standard deviations.

Spearman rank order correlations were done to detect relationships between cognitive performance and those symptoms that showed statistically significant improvement. Scatterplots were used for the interpretation of the relationships found.

Where possible, summary indices for cognitive domains were calculated to evaluate change when power is increased and the possibility of Type I error reduced. Composite scores were calculated for *memory* [verbal (RAVLT I-V) and visual (WMS I; WMS II)], *verbal expression* [naming (BNT) and fluency (COWAT)], *psychomotor functioning* (TMT-A; TMT-B) and *executive functioning* (EF) that was divided into two components according to the meaning of a higher score: EF-1 [Initiation and Switching (TMT-B) and Self-Monitoring (RAVLT - Errors & Repetitions)] and EF-2 [Planning and organisation (RCFT & CFOQS) and Abstract reasoning (Similarities)]. All composite scores were summed raw scores. The differences were compared between the experimental group and control group with the *t*-test for independent samples. However, while summed scores based on clutches of discrete tests provide good reliability, they do not convey neuropsychologically relevant information unless the scores are either so low or so high that the level of the contributing scores are obvious (Lezak, 1995).

The problems created by the large intragroup variations which so often characterise patients with schizophrenia (Lezak, 1995) were also evident in this study. Two outliers were identified on the basis of their MMSE scores being  $\leq 17$  indicating severe impairment or psychosis (Maruish, 2000). They were not excluded from the study as their exclusion did not produce any significant statistical difference.

### 3. Results

#### 3.1. Neuropsychological change from baseline to end point

There were no overall significant differences in neuropsychological function between the experimental (EPA) and the control (Placebo) group. In a few isolated tests the experimental group did significantly better at end point than the control group. Conversely, for other isolated tests the control group did significantly better at end point than the experimental group (Table 2).

Table 2

Mean change scores and significance of change between baseline and end point values for each patient group

Tests	Patients Given EPA (n=19)			Patients Given Placebo (n=20)		
	Mean Change	SD	P	Mean Change	SD	P
MMSE: Total (30)	0.842	2.410	0.1451	1.450	2.544	† 0.0196
MMSE: Orientation (10)	0.158	0.765	0.3800	0.500	1.469	0.1444
RAVLT: List A, Trial I	1.158	1.979	† 0.0201	1.000	1.487	† 0.0072
RAVLT: List A, Trial II	0.947	2.415	0.1044	0.950	1.317	† 0.0044
RAVLT: List A, Trial III	1.526	3.186	0.0512	0.900	1.804	† 0.0379
RAVLT: List A, Trial IV	1.316	3.622	0.1307	0.950	2.282	0.0782
RAVLT: List A, Trial V	1.526	4.287	0.1380	0.850	2.477	0.1413
RAVLT: List B, Trial I	0.842	2.713	0.1930	-0.300	1.750	0.4528
RAVLT: List A, Trial VI	0.263	3.588	0.7529	1.600	2.280	† 0.0054
RAVLT: Delayed, Trial VII	1.105	2.923	0.1167	1.650	2.134	† 0.0026
RAVLT: Total Words, □ (I-V)	6.474	12.721	† 0.0396	4.650	5.594	† 0.0015
RAVLT: Words Learned, (V-I)	0.368	3.700	0.6694	-0.150	2.254	0.7693
RAVLT: % Recall after B	-36.407	107.878	0.1585	5.913	61.398	0.6715
RAVLT: % Recall on Delay	23.686	62.884	0.1181	-3.777	46.643	0.6022
RAVLT: Adjusted score, (TP-FP)	2.158	9.720	0.3460	0.600	4.988	0.5969
RAVLT: Errors, □ (I-V)	-0.789	3.568	0.3476	-0.550	2.982	0.4197
RAVLT: Repetitions, □ (I-V)	4.053	8.189	† 0.0447	1.700	4.943	0.1405
WMS: Visual Reproduction I	4.895	5.626	† 0.0013	3.000	4.746	† 0.0108
WMS: Visual Reproduction II	3.842	5.347	† 0.0058	4.300	6.045	† 0.0049
RCFT: Copy	2.224	5.128	0.0750	1.363	4.464	0.1882
CFOQS: Organisation	-0.053	1.026	0.8256	-0.200	0.834	0.2967
TMT: A (Time in seconds)	36.000	96.754	0.1222	-13.200	51.255	0.2637
TMT: B (Time in seconds)	-104.133	214.054	0.0805	-61.143	185.231	0.2387
COWAT: FAS	1.895	6.951	0.2502	2.700	4.118	† 0.0086
SAWAIS-R: Similarities	0.474	2.245	0.3699	1.500	1.987	† 0.0032
BNT	1.316	2.689	† 0.0469	0.600	3.186	0.4101

† Marked differences are significant at  $p < 0.05$



A *t*-test for independent variables between mean change scores in the EPA and the Placebo group indicated no significant statistical differences between baseline and end point (see Table 3).

Table 3

Comparisons of mean change scores and significance among patients receiving EPA and patients receiving Placebo

Tests	EPA (n=19)	Placebo (n=20)	Effect Size	Analysis		
	Mean Change	Mean Change		t-value	df	P
MMSE: Total (30)	0.842	1.450	-0.245	-0.765	37	0.449
MMSE: Orientation (10)	0.158	0.500	-0.306	-0.905	37	0.371
RAVLT: List A, Trial I	1.158	1.000	0.091	0.283	37	0.779
RAVLT: List A, Trial II	0.947	0.950	-0.001	-0.004	37	0.997
RAVLT: List A, Trial III	1.526	0.900	0.251	0.760	37	0.452
RAVLT: List A, Trial IV	1.316	0.950	0.124	0.379	37	0.707
RAVLT: List A, Trial V	1.526	0.850	0.199	0.607	37	0.547
RAVLT: List B, Trial I	0.842	-0.300	0.512	1.570	37	0.125
RAVLT: List A, Trial VI	0.263	1.600	-0.456	-1.396	37	0.171
RAVLT: Delayed, Trial VII	1.105	1.650	-0.215	-0.667	37	0.509
RAVLT: Total Words, □ (I-V)	6.474	4.650	0.199	0.585	37	0.562
RAVLT: Words Learned, (V-I)	0.368	-0.150	0.174	0.531	37	0.598
RAVLT: % Recall after B	-36.407	5.913	-0.500	-1.516	37	0.138
RAVLT: % Recall on Delay	23.686	-3.777	0.501	1.554	37	0.129
RAVLT: Adjusted score, (TP-FP)	2.158	0.600	0.212	0.635	37	0.530
RAVLT: Errors, □ (I-V) *	-0.789	-0.550	-0.073	-0.228	37	0.821
RAVLT: Repetitions, □ (I-V) *	4.053	1.700	0.358	1.093	37	0.282
WMS: Visual Reproduction I	4.895	3.000	0.365	1.139	37	0.262
WMS: Visual Reproduction II	3.842	4.300	-0.080	-0.250	37	0.804
RCFT: Copy	2.224	1.363	0.179	0.560	37	0.579
CFOQS: Organisation	-0.053	-0.200	0.159	0.494	37	0.625
TMT: A (Time in seconds) *	36.000	-13.200	0.665	1.999	37	0.053
TMT: B (Time in seconds) *	-104.133	-61.143	-0.215	0.569	33	0.569
COWAT: FAS	1.895	2.700	-0.145	-0.443	37	0.660
SAWAIS-R: Similarities	0.474	1.500	-0.485	-1.514	37	0.139
BNT	1.316	0.600	0.244	0.756	37	0.454
PANSS (% Change)	13.161	3.139	0.729	2.278	37	0.029
ESRS (IV Dyskinetic Movements)	1.737	-0.100	0.935	2.912	37	0.006

Positive mean change reflects improvement in performance from baseline to end point except for \* Errors, Repetitions, TMT-A, TMT-B where a negative mean change reflects improvement.

Positive effect size indicates the power with which the EPA group shows more improvement than the Placebo group and visa versa.



As indicated by effect size, the power of the statistical differences varied widely. On 12 of the 25 independent neuropsychological test scores the EPA group improved more than the Placebo group. However, none of these improvements were statistically significant. For 13 independent neuropsychological test scores on which the Placebo group improved more than the EPA group, there was again no statistical difference. Thus no group improved more or less than the other group.

### 3.2. Composite neuropsychological test scores

Composite neuropsychological scores indicated no statistical differences between the EPA and Placebo group, as shown in Table 4. On the memory index, psychomotor functioning and executive functioning-1 the EPA group improved more than the Placebo group during the study duration. On verbal expression and executive functioning-2 the Placebo group showed more improvement than the EPA group. However, even with the reduction for the possibility of Type I error and with power increased (Benjafield 1994), no statistically significant difference in mean change was identified between the two groups.

Table 4

Composite scores of neuropsychological tests for each patient group

Areas	EPA		Placebo		Analysis			
	Mean Change (n=19)		Mean Change (n=20)		Effect Size	t-value	df	P
Memory Index	15.21	(16.02)	11.95	(11.18)	0.239	0.740	37	0.464
Verbal Expression	3.21	(7.79)	3.30	(4.40)	-0.015	-0.044	37	0.965
Psychomotor Functioning *	-89.60	(217.27)	-10.13	(234.14)	-0.352	-0.978	29	0.336
Executive Functioning-1 *	-100.80	(214.56)	0.75	(239.39)	-0.447	-1.241	29	0.225
Executive Functioning-2	2.65	(6.04)	2.66	(4.86)	-0.003	-0.010	37	0.992

Positive mean change reflects improvement in performance from baseline to end point except for \* Psychomotor Functioning, Executive Functioning-1 where a negative mean change reflects improvement.

Positive effect size indicates the power with which the EPA group shows more improvement than the Placebo group and visa versa, except on \* areas where a negative effect size indicates more improvement in the EPA group.

### 3.3. Correlations among neuropsychological tests and symptom improvement

A significant difference on the total Positive and Negative Symptom Scale (PANSS) score was found between patients receiving EPA and those receiving the Placebo (P=0.029). The dyskinesia subscore of the Extrapyrimal Symptom Rating Scale (ESRS) also improved significantly more in patients receiving EPA than those receiving the Placebo (P=0.006) (see Table 3).

Table 5

Spearman correlations among symptom severity (total PANSS score); dyskinesia movements (subscale of ESRS) and neuropsychological tests for each patient group

Test	PANSS Percentage Change		Dyskinesia Movements Change	
	EPA (n=19)	Placebo (n=20)	EPA (n=19)	Placebo (n=20)
MMSE: Total (30)	-0.33	0.09	-0.05	0.17
MMSE: Orientation (10)	0.03	0.15	0.13	-0.12
RAVLT: List A, Trial I	-0.007	0.02	0.01	0.10
RAVLT: List A, Trial II	-0.13	-0.24	-0.02	-0.38
RAVLT: List A, Trial III	-0.11	0.19	0.13	-0.05
RAVLT: List A, Trial IV	-0.17	0.11	0.05	0.17
RAVLT: List A, Trial V	-0.37	0.94	-0.08	0.35
RAVLT: List B, Trial I	0.39	-0.06	-0.14	-0.25
RAVLT: List A, Trial VI	0.27	-0.16	0.19	0.32
RAVLT: Delayed, Trial VII	0.004	-0.16	0.29	0.37
RAVLT: Total Words, $\Sigma$ (I-V)	-0.19	0.08	0.08	0.33
RAVLT: Words Learned, (V-I)	-0.42	0.08	-0.08	0.28
RAVLT: % Recall after B	† 0.51	-0.14	0.17	0.07
RAVLT: % Recall on Delay	-0.44	0.18	-0.11	-0.15
RAVLT: Adjusted score, (TP-FP)	-0.38	-0.01	-0.03	0.15
RAVLT: Errors, (I-V)	0.09	0.10	0.16	-0.05
RAVLT: Repetitions, (I-V)	0.12	0.16	0.22	-0.13
WMS: Visual Reproduction I	-0.42	0.08	-0.31	0.14
WMS: Visual Reproduction II	-0.34	† -0.45	0.05	† 0.47
RCFT: Copy	-0.03	-0.04	-0.14	-0.09
CFOQS: Organisation	0.45	0.29	0.14	0.30
TMT: A (Time in seconds)	0.23	-0.38	0.02	-0.13
TMT: B (Time in seconds)	0.03	0.15	0.40	0.18
COWAT: FAS	-0.19	-0.29	-0.07	0.17
SAWAIS-R: Similarities	-0.26	-0.06	0.06	-0.04
BNT	-0.12	0.36	0.11	-0.32

† P<0.05; Positive and Negative Symptom Scale (PANSS); Extrapyramidal Symptom Rating Scale (ESRS)

To examine the extent to which patients' performance on the neuropsychological tests were affected by their improvement on symptom severity and dyskinesia movements, the relationships were investigated (see Table 5). In the EPA group only one out of 25 independent neuropsychological test scores significantly correlated with symptom severity on the PANSS total



score (% change). Percentage recall after List B (retention for newly learned information) showed a positive correlation with symptom severity (PANSS) in the EPA group ( $r = 0.51$ ,  $P = 0.026$ ), but not in the Placebo group ( $r = -0.14$ ,  $P = 0.544$ ). There was a negative correlation between delayed visual reproduction and symptom severity (PANSS) in the Placebo group ( $r = -0.45$ ;  $P = 0.046$ ), but not in the EPA group ( $r = -0.34$ ;  $P = 0.151$ ).

Delayed visual reproduction showed a positive correlation with dyskinesia movement (ESRS) in the Placebo group ( $r = 0.47$ ;  $P = 0.038$ ), but not in the EPA group ( $r = 0.05$ ;  $P = 0.851$ ). There were no significant correlations among any of the neuropsychological test scores and the dyskinesia movement (ESRS) in the EPA group. In conclusion, most correlations were weak, with the exception of a few isolated relationships.



#### 4. Discussion

The objective of the present study was to evaluate the potential of eicosapentaenoic acid (EPA) to improve cognitive functioning in patients with schizophrenia. Findings in this study showed no evidence to support the hypothesis that EPA supplementation improved cognitive functioning in patients with schizophrenia.

Schizophrenia remains an illness that is difficult to treat. Neuroleptic benefits are predominantly limited to the positive symptoms, while the effect on negative symptoms and cognitive impairment are thought to be substantially less (Blyler and Gold, 2000).

Currently, the diet supplementation of EPA, an omega-3 essential fatty acid, is being investigated in the treatment of clinical symptoms of schizophrenia. Early indications suggest a trend towards improvement, although nonsignificant, in both positive ( $P = 0.216$ ) and negative ( $P = 0.14$ ) symptoms. The percentage change score on the general PANSS improved significantly ( $P = 0.044$ ) as did the percentage change score on the total PANSS ( $P = 0.029$ ); indicating improvement of the psychiatric symptoms (Emsley et al., unpublished results). It was hoped that an equal benefit would be found in the third symptom feature in schizophrenia; namely cognition. However, this study failed to find any improvement in cognitive functioning, for no change on any of the neuropsychological tests were statistically more significant in those patients using EPA.

The neuropsychological assessment showed no significant improvement from baseline to end point, indicating no improvement in cognitive functioning. This may imply that cognitive dysfunction is an independent feature of schizophrenia, consistent with the literature suggesting cognitive impairment to be a distinct construct (Addington, 2000). An alternative explanation is that EPA has the potential to elicit improvement in cognitive function, but that there were research design flaws and limitations.

It is not always possible to find appropriate alternative tests for re-testing, in the hope to minimise practice effect. Studies have demonstrated that in patients with schizophrenia, intellectual quotient (IQ) is often about 1 standard deviation below average (McGurk, 1999). Assessing intelligence may have contributed in the interpretation of neurocognitive results, because patients with cognitive impairment tend to score differently from healthy controls on some repeated tests. It may be that impaired brains are less able to benefit from practice effect or that premorbidly highly functioning brains may already have been at the ceiling scores at baseline, and be prejudiced against in the recording of practice effect gains (Laws and Kondel, 1998).



The assessment of premorbid intellectual ability and neuropsychological damage would have been useful in another way. It may have identified patients with permanent neuropsychological damage, and thus account for the findings of no cognitive improvement in this study.

A broader battery with additional neuropsychological tests may have been useful in eliciting cognitive impairment [e.g. Continuous Performance Test (Cadenhead and Braff, 2000), Digit Span (subtest of the WAIS-R) (Stone et al., 1998) for assessing attention and concentration, and the executive tasks of the Wisconsin Card Sorting Test, Category Test and Stroop Color Word Interference Test (Palmer and Heaton, 2000)].

In general the EPA group showed a greater intragroup variation in mean change from baseline to end point on the neuropsychological tests. Large intragroup variation may influence observation of change and should be considered in these results. The placebo group was more homogeneous in terms of change over the study period. The Welch statistical test was used to correct for these large differences in standard deviations between the two groups. Although, this made hardly any difference to the significance of the cognitive change over time, more homogenous and individually matched groups (e.g. age, MMSE) may be of use in further studies.

There are limitations to this study that may account for these findings. (1) The trial duration may not have been adequate. This study assessed the short-term effects of EPA, whereas complex cognitive functions (e.g. executive functioning) may take longer to show improvement (Keefe et al., 1999). (2) The side effects of the different neuroleptic medications that patients were stabilised on, could have provided potentially misleading results. Cognitive functioning is also differentially affected by neuroleptics (Goldberg, 1993), with clozapine identified as the first medication for schizophrenia to demonstrate the ability to improve cognitive functioning (McGurk, 1999), and ideally all patients should have been on the same drug regime and on similar dosages. (3) The age of the study population ranged from 17.10 to 69.12 years, thus including patients that may have showed age-appropriate cognitive deterioration. A study with exclusion criteria for subjects >50 years may have been more appropriate.

Future research should consider the following study exclusions: An age limit of 50 years to take age-appropriate deterioration into account, baseline intellectual assessment to control for patients with permanent neuropsychological damage that would not be able to improve, and MMSE cut-offs to exclude patients with dementia. The appropriate sample size is crucial in that it affects the



power of the study to reject or accept the null hypothesis (Keefe et al., 1999), by giving EPA an adequate opportunity to have an effect. More long-term studies (>20 weeks) that allow for cognitive responses that may extend for months after the initiation of treatment, as documented in some studies (Keefe et al., 1999), are needed. The exclusion of patients with positive symptoms at time of testing would be helpful in that the influence of the positive symptoms on results will be null.

Practice effect should be considered by assessing matched patient groups in terms of age, gender and educational level, and comparing them to normal controls. Standardised medication regimes of patients should be included in future studies to control for the variable effect medication has on cognitive functioning.

First onset versus chronic patients with schizophrenia should be studied to determine whether the effect of EPA differentiates between these two groups. However, in a review of 15 studies assessing the course of neuropsychological deficits in patients with schizophrenia, no support for a decline in cognitive functions was found, thus not reporting schizophrenia as a degenerative process, but rather a static encephalopathy (Rund, 1998).

Premorbid low intellectual ability versus high premorbid functioning patients with schizophrenia should be compared in terms of the effect of EPA on their cognitive functioning. Results in this study regarding the effect of EPA on cognitive functioning varied widely and may have influenced the results.

No validated brief neurocognitive batteries are available for this population group (Velligan and Miller, 1999). More comprehensive test batteries that are more sensitive for the specific deficits in patients with schizophrenia need to be developed. In the South African context, English, Afrikaans and Xhosa (in the Western Cape) validity comparable tests must be developed.

In conclusion, this study showed no evidence to support the hypothesis that EPA supplementation improved cognitive functioning in patients with schizophrenia. The prominence of cognitive impairment in schizophrenia and its associations with negative symptoms, social functioning and outcome of the illness suggest that it may play an important role in determining the success of psychosocial rehabilitation (Mueser, 2000). Despite the limitations, the present study is an important step towards the investigation of the potential of EPA to improve cognitive functioning in patients with schizophrenia and helps to identify areas for future research.

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