

Phosphatidylserine (PS) and Age-Related Cognitive Decline (ARCD)

1. Age-Related Cognitive Decline (ARCD)

Age related cognitive decline (ARCD) [1] is the scientific term for memory loss in elderly people who are clinically healthy. It is a physiological process associated with aging, not a disease, and occurs during middle life or later. Many people who are clinically healthy find as they get into their forties or fifties, sometimes even as early as their thirties, that they are losing mental sharpness. They have more trouble to keep track of their glasses and their keys. They have increasing difficulties in remembering names and matching names to faces. After reading important material, they forget it within minutes. One estimates that more than 40 percent of people aged 50 to 59 show ARCD, as do more than 50 percent of people aged 60 to 69, and even a greater proportion of those past 80.

The decline in memory is significant, approximately half of our memory capabilities at age 25 are lost at ages 50-59, and even up to three quarters at age 70+.

Decline in memory with advancing age

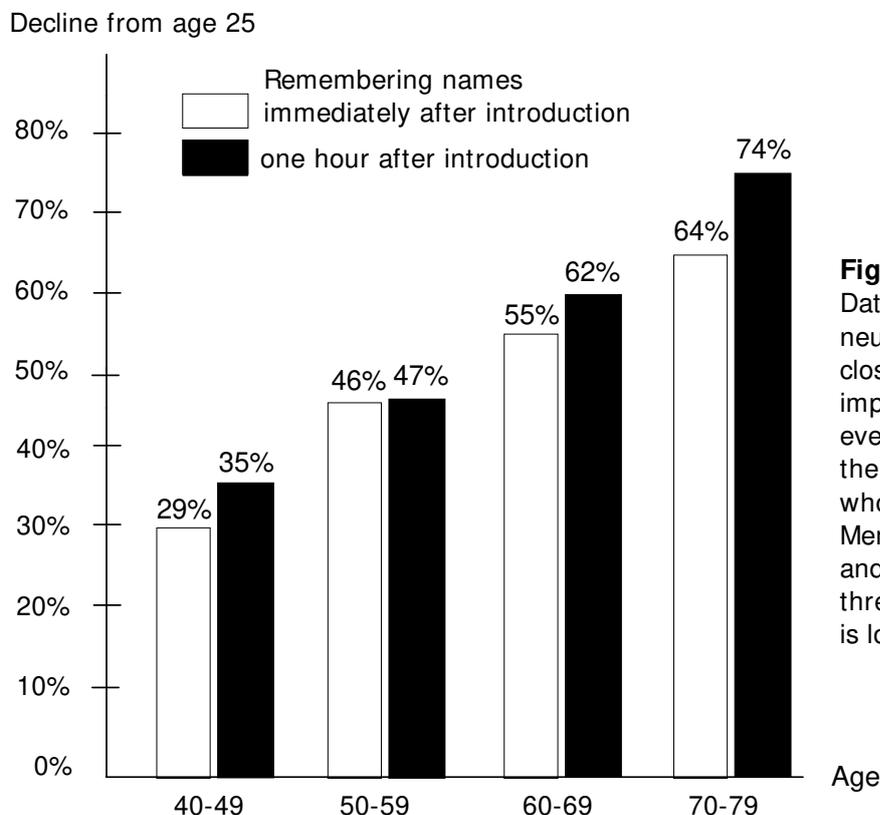


Fig.1 Data from an objective, neuropsychological test that closely simulates an extremely important memory task in everyday life, remembering the names of persons to whom one is introduced. Memory declines with age and for example up to three quarters of our memory is lost at age 70+ [1].

Without question, the individuals suffer worst from ARCD have serious trouble on the job and in their personal life: they aren't able to function at anywhere near the level they used to. Causes of ARCD are diverse and based on biochemical and structural changes: the total brain mass decreases (by up to 100 g) with age and even more serious is the decrease in synaptic density and the death of nerve cells, changes in lipid composition and content in cell membranes, decrease in enzyme activity as well as reduced synthesis and release of neurotransmitters.

Those changes can be categorized in three theories of aging:

1. Membrane Hypothesis of Aging

Aging results in changes of membrane lipid composition, the cholesterol content increases, whereas the phospholipid content decreases. This results in alteration of the normal viscosity of cellular membranes and hence in a loss of enzymatic activities and transport mechanisms. Those changes result in an impairment of cerebral functions, e.g learning and memory.

2. Morphological Hypothesis of Aging

Aging results in the death of nerve cells as well as in a decrease of connections between brain cells (dendritic spine loss). The extend of synaptic loss has been shown to correlate with the degree of cognitive impairment.

Aging results in dendritic spine loss

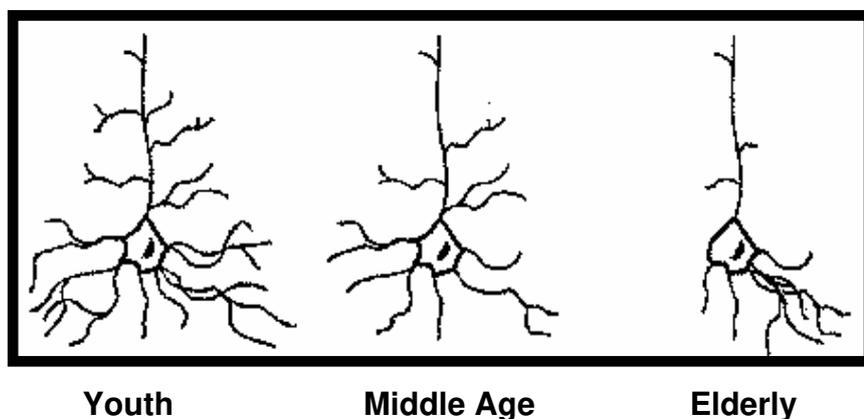


Fig.2. Dendritic spine loss with age [2].

3. Cholinergic Hypothesis of Aging

Aging results in reduced synthesis and release of neurotransmitters. Multiple neurotransmitter deficits have been implicated in age-related memory loss. Specific populations of cerebral neurons above all, cholinergic, undergo degenerative changes, which have been shown to correlate with the degree of cognitive impairment.

2. Animal studies on the effect of PS on the three theories of aging

1. Membrane Hypothesis of aging

Phosphatidylserine supplementation is able to restore the fluidity and composition of membranes by normalizing the cholesterol to phospholipid ratio. Undesirable ratios of old animals can be restored to levels common for young animals by PS supplementation [3].

PS normalizes Cholesterol to Phospholipid ratio

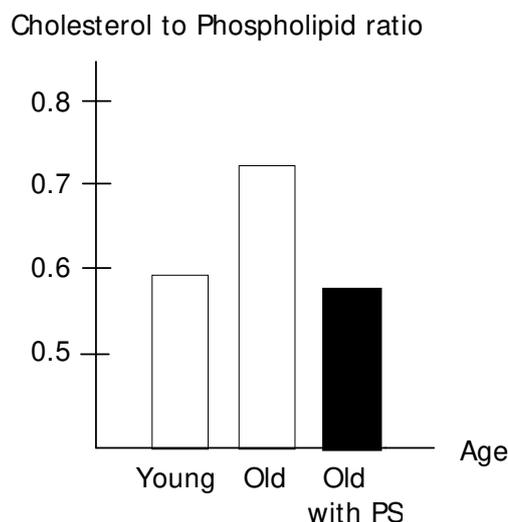


Fig.3

PS is able to normalize the Cholesterol to Phospholipid ratio of old animals to levels common for the young [3], hence restoring membrane fluidity and composition.

Several studies showed that PS is able to restore enzymatic activity. PS activates protein kinase C in the cerebral cortex of aged rats [4], an enzyme which is part of the neurotransmitter signaling cascade within neuronal cells. Tyrosine hydroxylase [5], acetylcholinesterase [6] and the sodium-potassium activated ATPase are also

activated by PS [6,7]. This latter enzyme regulates the sodium-potassium gradient and the calcium-magnesium gradient between the interior and the exterior of the cells and thus PS supplementation helps to maintain the neuronal excitability and message transfer within the cells during old age.

2. Morphological Hypothesis of Aging

The dendritic spines of hippocampal pyramidal cells, the post-synaptic target of the excitatory input, have been proposed as a substrate for information storage, the hardware for cognitive processes. Age-dependent spine loss in pyramidal neurons has been reported in the human brain. Moreover, the extent of synaptic loss has been shown to correlate with the degree of cognitive impairment. Chronic treatment with phosphatidylserine prevents the age-related reduction in dendritic spine density in rat hippocampus [8].

Mean spine density with and without PS supplementation

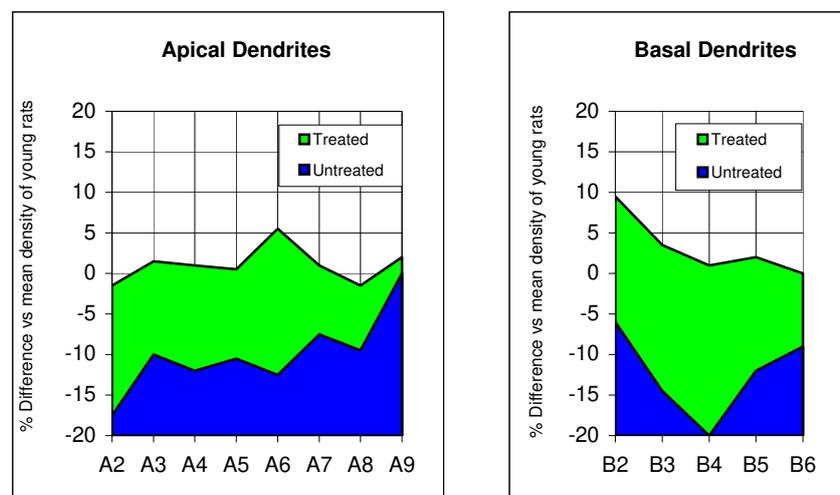


Fig.4. Percentage differences of mean spine density on basal (B2-B6) and apical oblique (A2-A9) dendritic orders, between 3-month-old rats (assumed as baseline, young = 0) and 27 months old rats with or without PS supplementation

3. Cholinergic Hypothesis of Aging

The neurotransmitter acetylcholine is synthesized by the enzyme **choline acetyl transferase (ChAT)** from acetyl coenzyme A and choline. After release, acetylcholine

is inactivated by hydrolytic cleavage by the enzyme acetylcholinesterase. 30% of the total acetylcholine brain pool is used per minute. The turnover rate in the brain is at least 10 times higher than that of all other neurotransmitter. This clearly shows that a fast resynthesis rate has to be available for proper functioning of the brain. Old impaired rats do have a reduction of ChAT positive neurons in the forebrain (cerebral cortex) and hence a reduced capability of producing the neurotransmitter Acetylcholine. Phosphatidylserine supplementation counteracts the reduction of ChAT positive cells and is able to restore the values to a level comparable to young animals [9].

PS Supplementation restores neurotransmitter synthesis

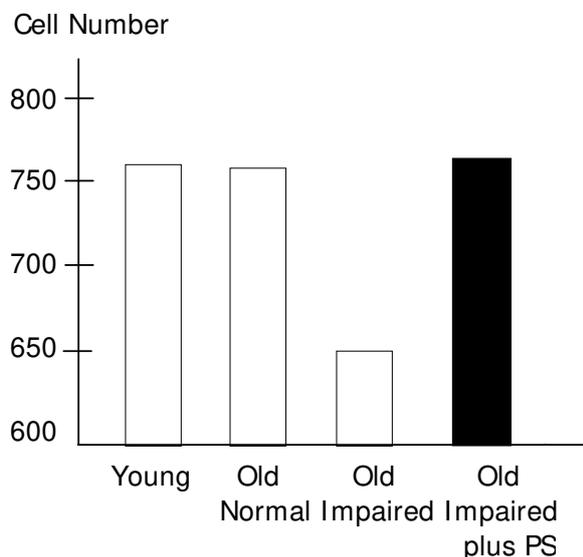


Fig.5

The number of ChAT positive cells, cells able to produce the neurotransmitter acetylcholine from choline and acetyl coenzyme A, is decreased in old impaired animals. PS supplementation is able to restore the number of ChAT positive cells, hence having an influence on the synthesis and release of this essential brain neurotransmitter [9].

Phosphatidylserine restores acetylcholine release by maintaining an adequate acetylcholine supply. PS is able to increase the availability of endogenous choline for de novo synthesis and release [10-14]. Similar treatments with phosphatidylcholine had no effect [15]. In addition, PS restores dopamine release [16] and promotes glutamatergic neurotransmission [17]. In fact, dopaminergic, glutamatergic and cholinergic neurotransmission play an essential role in learning, memory and other cognitive functions in man.

PS Supplementation restores neurotransmitter release

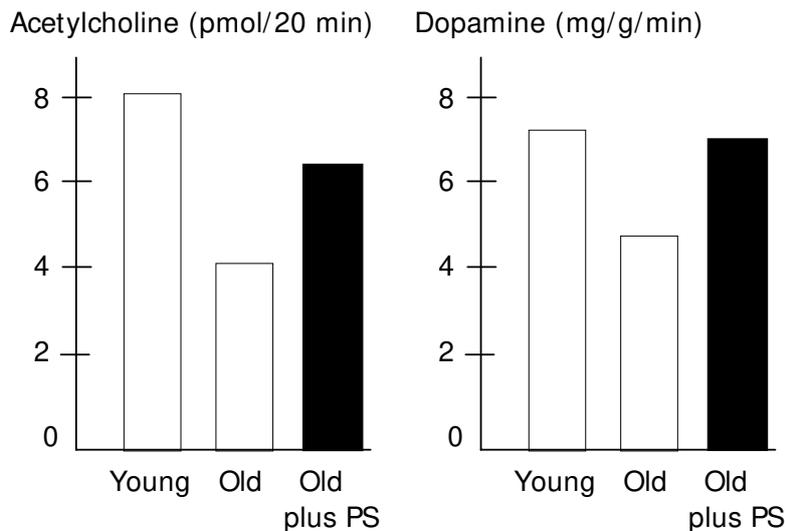


Fig.6

PS supplementation restores the release of the neurotransmitters acetylcholine and dopamine. The release of both neurotransmitters is decreased with age [9-16].

3. Animal efficacy studies with PS

Aging, in both human and animal species, is characterized by a decay of learning and memory function. Learning and memory deficits in senescent animals are widely used as a tool to evaluate the potential benefit of brain nutrients. PS was investigated in different animal tests of age-related memory impairment [18-26] and showed continuously significant improvements.

Morris Water Maze Test

The Morris water maze test [27] measures learning/memory in a place-navigation test. A large circular pool filled with water is used as the test apparatus. The water is darkened with brown food coloring and maintained at a certain temperature. Four equidistant points at the edge of the pool are designated as start positions and a transparent platform was fixed 1 cm below the surface. The rats are trained in two blocks of four trials each, using all four starting positions in a random sequence. If the rat failed to reach the hidden platform within 120 seconds, it was placed there by the investigator.

Aged rats (21-24 months) were investigated and performance was compared to young rats, 5 months old. The age-dependent decline is not uniform throughout the population since rats, like humans, develop cognitive impairments to a variable degree. Rats were screened in the Morris water maze test to select aged impaired and aged non-impaired rats. Aged impaired rats were matched by mean performance

scores and then assigned to a PS or control group. After the initial screening the rats were tested again after 7 and 12 weeks of oral PS supplementation.

Aged impaired animals did not reach the optimum performance level of young rats even after extensive training. This persistent learning deficit can essentially be ascribed to reduced spatial accuracy in locating the hidden platform site, as indicated by lack of efficient searching behavior. PS treated rats showed a significant decrease in mean escape latency and improved performance at both test weeks.

PS Supplementation reverses age-related cognitive decline

Mean escape latency in seconds

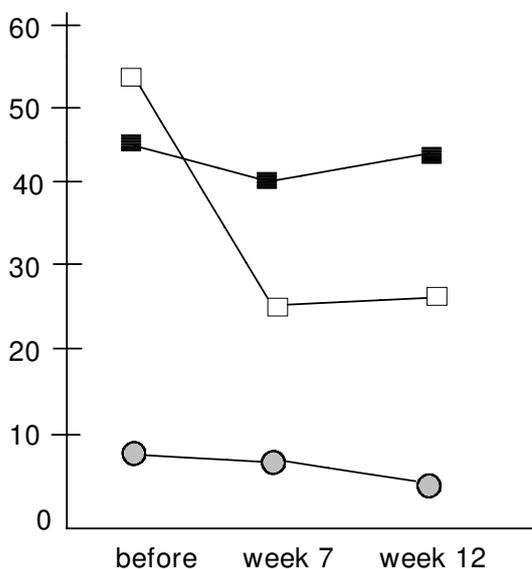


Fig.7

Mean escape latency over the last four trial blocks during screening (before), week 7 and week 12 [18]. PS supplementation significantly improves performance in the Morris water maze test.

- Old Impaired plus PS
- Old Impaired plus Placebo
- Young

Avoidance Learning Tests

The efficacy of PS was investigated in different passive and active avoidance tests [18-26], showing that PS is effective in reversing age-related decline of brain functions. In addition, long-term oral PS supplementation is able to prevent the development of certain brain deficits. Rats supplemented with PS for 17 months, starting at the age of 2 months were investigated and compared to rats without PS supplementation of the same age. At the age of 19 months the control rats showed a decrease in the capability to learn a conditioned avoidance response. Chronic PS supplementation, however, completely prevented the decay in active avoidance

acquisition. Old, chronic PS supplemented rats showed no difference to the young group.

Chronic PS Supplementation prevents decay in brain functions

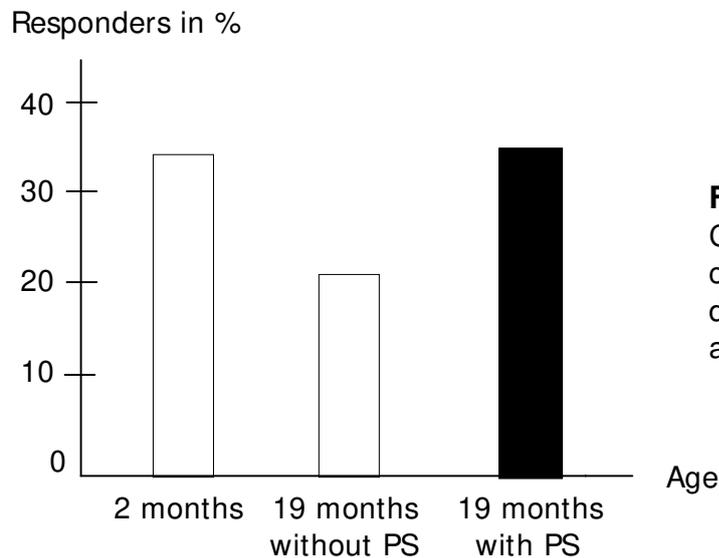


Fig.8
Chronic PS supplementation completely prevents the age-related decay of brain functions (active avoidance acquisition [19]).

4. Human clinical trials

The efficacy of PS supplementation was proven in numerous randomized double-blind placebo controlled clinical trials [28,29,32-40]. The duration of the trials varied from 6 weeks up to 6 months and the common daily dosage was 300 mg, but also doses as low as 100 mg were investigated. People from all over the globe (Europe: Italy, Germany, Belgium; Middle East: Israel, America: USA) were investigated in clinical trials with up to 494 persons in a single trial. The efficacy of PS supplementation was investigated using different performance tests related to learning and memory tasks of daily life.

Examples of human clinical trials

Cenacchi et al. [38] performed a double-blind clinical trial on the efficacy and safety of oral phosphatidylserine supplementation vs. placebo (300 mg per day for 6 month) in a group of persons with cognitive impairment. In this multicenter study (23 locations) a total of 494 elderly patients (age between 65 and 93 years) with moderate to severe cognitive decline were recruited. Due to 69 drop outs 425 persons were used for the statistic evaluation. Statistically significant improvements

in the phosphatidylserine treated group compared to placebo were observed in terms of behavioral and cognitive parameters. Highly significant results could be achieved, e.g. in Total Recall ($p=0.008$), Long Term Storage ($p=0.008$), Long Term Retrieval ($p=0.004$), and Long Term Retrieval Consistent ($p=0.007$). In addition, clinical evaluation and laboratory tests demonstrated that PS was well tolerated. These results are clinically important since the patients were representative of the geriatric population.

Crook et al. [35] treated 149 persons meeting the criteria of Age-Associated Memory Impairment for 12 weeks with 100 mg of Phosphatidylserine or Placebo. Investigated were Name/Face Acquisition, Name/Face Delayed Recall, Facial Recognition, Telephone Number Recall and Misplaced Objects Recall. For all parameters significant improvements ($p=0.05$ to $p=0.001$) could be achieved by phosphatidylserine supplementation. Persons scoring worst in the starting test showed the best improvement.

Early studies have been performed with PS derived from the brains of cattle (bovine cortex PS). In the interest of safety, all studies with bovine-derived PS were stopped after BSE (Mad Cow Disease) was first seen among cattle in England. Degussa BioActives (Lucas Meyer) introduced soy-derived PS under its trademark name LIPAMIN-PS. Animal [41-43] and human clinical trials [1,39,40,44] proved that soy-derived PS is as efficacious as bovine-derived PS.

12 weeks of supplementation with 300 mg of LIPAMIN[®]-PS (50 persons, mean age 60.5 years, 52% female) showed that the effects of LIPAMIN[®]-PS and bovine derived PS (BC-PS) are comparable [1], even slightly favoring the soy-derived LIPAMIN-PS.

LI PAMIN-PS is as effective as Bovine Cortex PS in humans

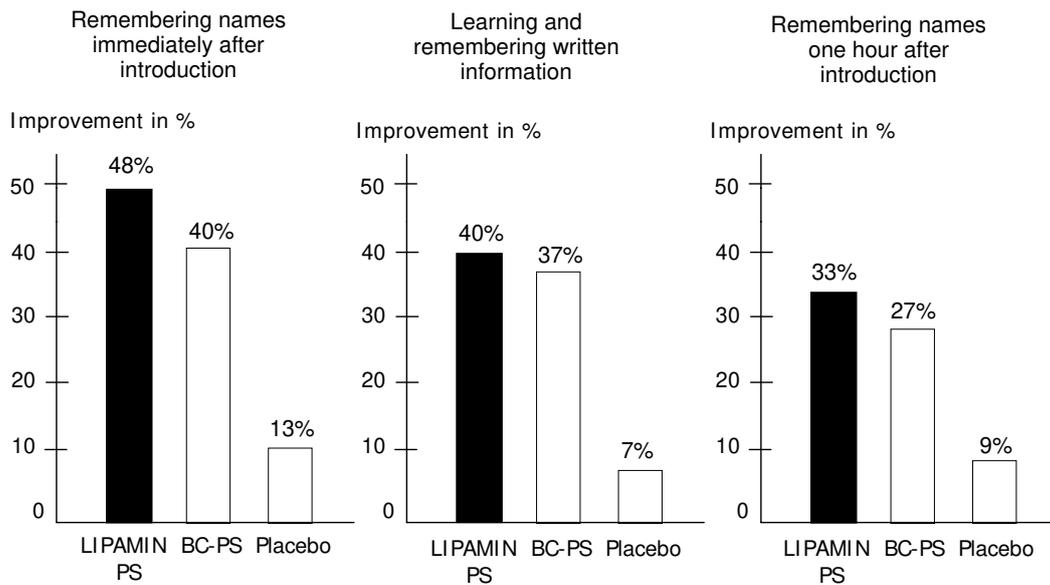


Fig.9
The efficacy of LIPAMIN-PS (soy-derived) is not only comparable to bovine-derived PS (BC-PS), statistically significant difference even favor LIPAMIN-PS [1].

Most striking are the effects of LIPAMIN[®]-PS on the ability to learn and remember names, here an age-related reversal approaching 14 years was observed. That is, a 66-year-old individual performs like a 52-year-old individual after 12 weeks of LIPAMIN[®]-PS treatment.

Efficacy of LI PAMIN-PS beyond those of Placebo

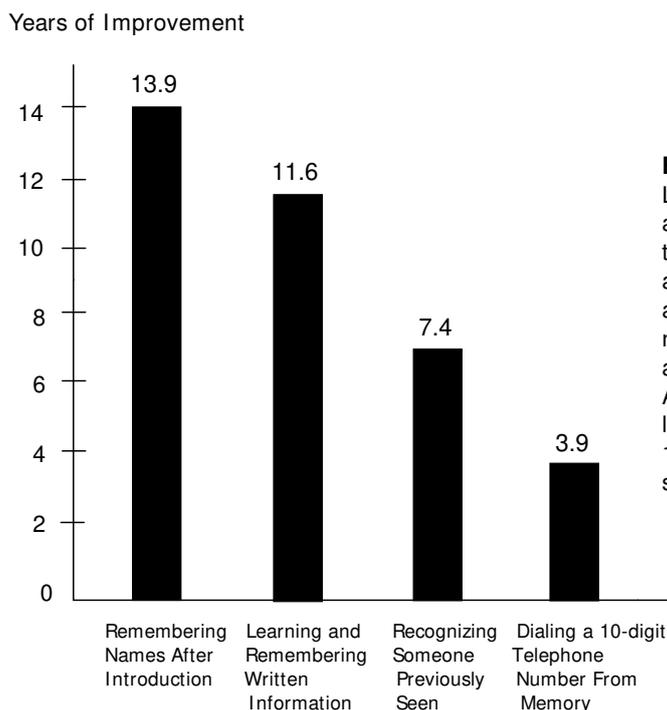


Fig.10
LIPAMIN-PS is able to reverse normal age-related memory loss such as various tasks of everyday life. Most striking are the effects of LIPAMIN-PS on the ability to learn and remember names. An age-related reversal approaching 14 years was observed. A 66-year old individual performed like an 52-year-old individual after 12 weeks of LIPAMIN-PS supplementation [1].

6. Dietary Sources, Daily Intake and Nutritional Undersupply of PS

Phosphatidylserine can be found in meat and fish, mainly innards such as brain, liver and kidney. Only small amounts of PS can be found in dairy products or vegetables with the exception of white beans.

Food	PS-Content in mg / 100 g
Meat	
Bovine Brain	713
Innards (average value)	305
Spleen (Pig)	239
Kidney (Pig)	218
Poultry (Leg)	134
Poultry (average value)	110
Poultry (Breast)	85
Beef	69
Pork	57
Liver (Pig)	50
Fish	
Mackerel	480
Herring	360
Eel	335
Tuna	194
Crayfish	40
Cod	28
Dairy	
Milk (3.5% Fat)	1
Milk (1.5% Fat)	0.5
Others	
Beans	107
Whole Grain	20
Rice (unpolished)	3

Table 1. PS content in different foods [45].

Various key historical developments resulted in a significant decrease in daily PS consumption during recent years, including changes in consumer attitudes (e.g. rejection of innards), increased awareness of healthy food (e.g. low fat, low cholesterol and reduced meat diets), and different food crises such as BSE (mad cow disease) or foot and mouth disease. To make matters worse, modern production of fats and oils decreases the natural phospholipid content of foods, subsequently, our daily intake of PS is also reduced.

Food	Consumption per person on a yearly basis 1986	Consumption per person on a yearly basis 2000
Innards	2.0 kg	1.0 kg
Beef	15.7 kg	9.7 kg
Pork	43.1 kg	39.6 kg
Poultry	6.0 kg	9.3 kg

Table 2. Changes in the meat consumption [46].

If we consider a suggested weekly diet of 3-4 servings of meat (100-200 g), 1-2 servings of fish (150-200 g), 3-4 servings of pork sausage and 2-3 eggs, plus 250 ml of milk and 1-2 slices of cheese each day, the typical daily intake of PS would be approximately 130 mg [47]. However, looking at the actual Western diet, we find that far more beef, pork, and poultry is consumed than fish. A diet rich in meat results in a daily PS intake of approximately 180 mg.

Daily PS Intake 1980ies	Daily PS Intake today diet rich in meat	Daily PS Intake today reduced fat diet	Daily PS Intake today Vegetarians
250 mg	180 mg	100 mg	< 50 mg

Table 3. Changes in PS consumption [47].

It is estimated that the nutritional undersupply of PS, considering the average diet, varies from 70 to 150 mg daily; a vegetarian diet may lack even more at 200 to 250 mg daily, compared to the 1980ies. Given this simple analysis, it becomes clear that

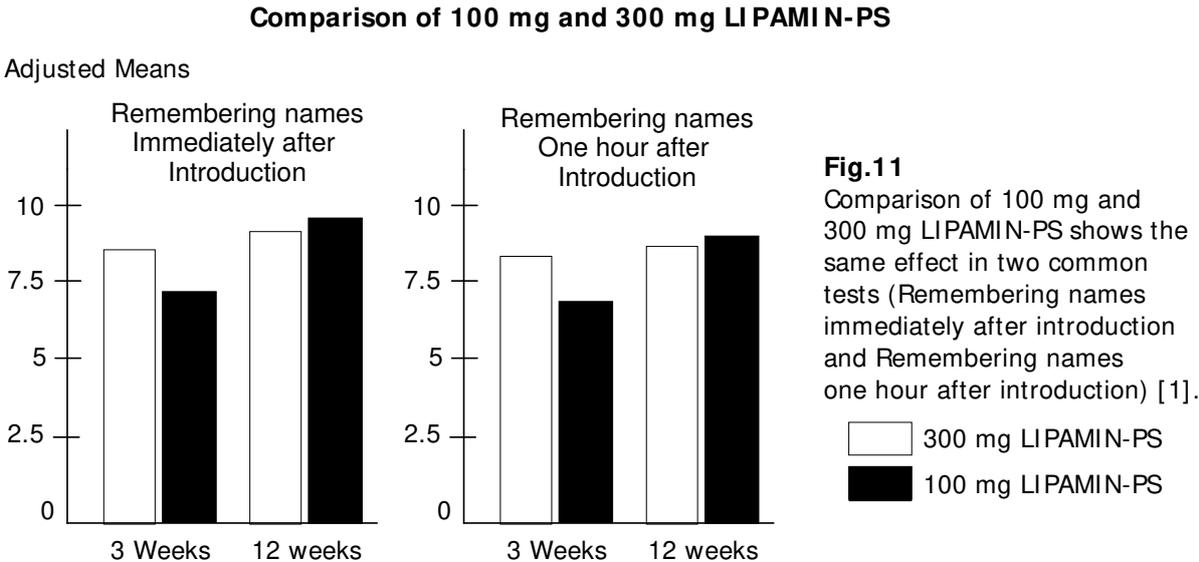
supplementation of our daily diet by 100 to 300 mg of pure PS is indicated, especially for vegetarians, persons using a low fat and/or low cholesterol diet, and the elderly. The reduced PS consumption in our modern eating habits warrants that this vital substance should be taken in order to maintain proper physical health and to improve mental performance.

7. Suggested Daily intake

300 mg is the common daily dosage and this amount has proven efficacy in double digit human clinical trials with up to app. 500 hundred persons involved and in application periods from 6 weeks to 6 months.

A study involving 12 persons addressed the question, if the same effects seen with 300 mg LIPAMIN-PS can be attained with a lower dose of 100 mg. Two tests, remembering names immediately after introduction and remembering names one hour after introduction were used to compare the effects after 3 and 12 weeks.

The effects seen after 3 weeks of supplementation favor the 300 mg group, although the differences were not statistically significant. The effects of 300 mg LIPAMIN-PS and 100 mg LIPAMIN-PS were the same after 12 weeks, suggesting that the optimal dosing might begin at 300 mg, then diminish to 100 mg after a month or two.



8. Summary

Age-Related Cognitive Decline may no longer be seen as inevitable. With almost 3,000 total research papers published, of which more than 60 were clinical studies on humans, Phosphatidylserine is the proven number-one brain booster. By improving membrane functions in cells throughout the brain, PS seems to boost many nerve transmitters while simultaneously improving their coordinated effects across the entire brain. LIPAMIN-PS has clearly shown it can turn back the clock on brain decline.

9. References

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