The Influence Of Antidepressants on Tumor Size and Cognition in Patients With Brain Cancer

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Abstract

Recent literature has shown that certain SSRIs like Fluoxetine have oncostatic effects on tumors in various types of cancers. Research has also found that a larger tumor size is associated with lower cognitive performance. Assumed that this oncostatic effect as a result of SSRIs exists, relative cognitive improvement could be inferred. This study aimed to show the oncostatic effect of SSRIs by looking into a group of brain cancer patients taking antidepressants. Thirty-seven participants were matched with an equally sized control group on sex, age, education level and on brain cancer subtype. Groups were compared over time on cognitive performance and survival rate. Tumor size was also measured using an MRI at T0. The participants were monitored over a 12-month period, and assessed with the CNSVS cognitive test battery at three points in time (T0, T3, T12). Survival rate was also calculated over these three points. The main questions posed in this study were: Is there an effect of antidepressants on cognitive performance? And do antidepressants have an effect on survival rate and tumor size? Little significant results were found in this study on all three variables, showcasing that it is vital for future research to have a larger sample size, and to focus on a single SSRI.

Keywords: Antidepressants, SSRI, serotonin, brain cancer, cognitive performance, tumor growth, oncostatic effect

Introduction

Serotonin as target of Antidepressants

Serotonin is commonly known as ‘the happy hormone’. This monoamine neurotransmitter, also known as 5-hydroxytryptamine (5-HT), is involved in multiple processes of the brain. These processes include but are not limited to memory, mood, sleep, hunger, wound healing, nausea, bone health, and sexual desire (Cleveland Clinic Website, 2022).

As a *neurotransmitter*, serotonin is almost exclusively synthesized in the raphe nuclei (Figure 1A), a brain region located in the brainstem (Berger et al., 2009). However, serotonin as a whole is not exclusively synthesized in the Central Nervous System (CNS). About 95% of serotonin is actually produced in the gut (where it is classified as a *hormone*), where it is also known as peripheral serotonin or Gut-Derived Serotonin (GDS) (Gershon & Tack, 2007; Walther et al., 2003). GDS is known to be important in regulating all sorts of processes, e.g. metabolic homeostasis and β-cell mass promotion, which helps balance glucose levels through insulin production (El-Merahbi et al., 2015). Serotonin in both the CNS and Peripheral Nervous System (PNS) has a large role to play in our physical and mental well-being, but we still do not understand all underlying mechanisms. It might therefore not come as a surprise that serotonin-affecting drugs are still widely researched. Because serotonin can not cross the blood-brain barrier (BBB) nor the blood-spinal cord barrier (BSPB) (Berger et al., 2009), psychological serotonin studies have mostly focused on CNS serotonin until quite recently. In contrast to CNS serotonin, GDS would not be assumed to impact brain and behavior as much as serotonin in the CNS. This is due to the BBB and BSPB stopping this GDS from directly entering the brain. This is one of the reasons why there is still a lot of ground to cover in order to better grasp a full understanding of this versatile monoamine.

As the gut is the largest serotonin producer in the body (Gershon & Tack, 2007; Walther et al., 2003), a logical next step would be to turn towards the digestive track's Enteric Nervous System (ENS) for serotonin research and its effects on the body. But as we know, there are various aspects that link the ENS and the CNS. The multifactorial link between Irritable Bowel Syndrome and Depression (Cleveland Clinic Website, 2022; Mudyanadzo et al., 2018; Ballou & Keefer, 2017) demonstrates a strong interrelation between the two. Another connection between the ENS and CNS is the nervus vagus, the longest cranial nerve in the body which runs all the way from the brain to the large intestine (Powley, 2000). Recent studies show that the ENS and CNS may be more linked than previously thought, with alterations in gut microbiota thought to influence various neurological disorders including: Stress, autism, depression, Parkinson's disease, and Alzheimer's disease (Kim et al., 2018). With this strong relationship in mind, and considering ongoing research on these topics, it is likely that more links could be discovered in the future. It is important to note that serotonin affects more than just the brain.

Antidepressants (ADs) have been used since as early as the 1950s (López-Muñoz & Alamo, 2009). As medicine improved, ADs and their subtypes evolved as well. They improved from rudimentary medication with serious side-effects like acute and chronic liver damage, psychosis and neuropathy (Pleasure, 1954; O'Connor, 1953), to the more modern ADs that are prescribed today. While these can still show side-effects like feeling nervous, feeling sick, indigestion, loss of appetite, and insomnia (NHS Website, 2021; Predictable et al., 2006), these are by comparison less severe than those of their predecessors, and are far safer in overdose (Bruggeman & O'Day, 2022; Harrigan & Brady, 1999). The most commonly prescribed ADs of today, Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs) and Serotonin-noradrenalin Reuptake Inhibitors (SNRIs) all influence serotonin in one way or another. ADs are, as the name suggests, most often prescribed for the treatment of depression.

However, ADs can be prescribed for various other issues, for example: Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD), Panic disorder, severe phobias, bulimia, and Post Traumatic Stress Disorder (PTSD). The first published paper linking depression to serotonin as a neurotransmitter (Coppen, 1967) was groundbreaking, stating that serotonin played a key role in depression. This cascaded into more research, resulting in the first paper about a still widely used AD called Fluoxetine being published in the 1970s (Wong et al., 1974). Most modern ADs influence serotonin, but there is still a lot of ongoing research to clarify the exact how and why of the mechanics behind these medications. A population especially vulnerable to mental health issues treated by the aforementioned ADs, is brain cancer patients (Ng et al., 2018; Akechi et al., 1999).

Antidepressants and Cancer

A seemingly unrelated subject that *is* studied at an overwhelming scale, is cancer and its treatments. More than 10% of all cancer patients struggle with depression (Smith et al., 2015). Cancer is also the single most-researched disease in the USA costing around $7.3B USD in 2021, with around $7.6B USD estimated for 2022 (NIH Website, 2021). Cancer is also the most deadly disease in the USA after heart disease, at around 600.000 deaths per year (CDC Website, 2022). Cancer is one of the most complex diseases in the world, but what if serotonin could have an effect on the treatment of tumors? An exploration into the body's biochemistry is needed to better understand this possibility.

A number of studies have already shown intriguing discoveries showcasing an inhibitory role of ADs in regards to cancer cell growth (Geeraerts et al., 2021; Schneider et al., 2021; Sarrouihle et al., 2015; Amelio et al., 2014; Kannen et al., 2011; Coogan et al., 2009; Xia et al., 1999). These studies have mostly focused on effects of ADs on cancer outside of the CNS, which is where GDS is affected more than CNS serotonin.

ADs also affect enteric neurons (Sjöstedt et al., 2021) by blocking GDS reuptake, thereby influencing the ENS. The main goal of most modern ADs, namely blocking serotonin reuptake, is not the only useful effect of these drugs. ADs seem to be a promising avenue to research with regards to carcinogenesis. Several studies show that SSRIs can inhibit tumor growth, through different pathways. Schneider et al. (2021) shows that the blocking of GDS reuptake through SSRIs inhibits tumor growth in murine tumor models. These murine models had an intentionally created a certain hormone deficit which caused the mice to synthesize less serotonin, which resulted in inhibited tumor growth (Kuhn & Hasegawa, 2020). This study also showed that these modified mice showed an enhanced accumulation of certain T-cells, whose main function is to recognize and kill infected cells like cancer cells (Demers et al., 2013). As a result of this T-cell accumulation, more cancer cells could be killed- therefore regressing cancer growth.

In another study, building blocks for chemicals called Serine and Glycine (typically consumed by tumors) (Amelio et al., 2014)) are also shown to be inhibited by certain SSRIs, namely Sertraline and Thimerosal. These SSRIs are shown to decrease anti-tumor activity in breast cancer mouse xenografts (Geeraerts et al., 2021). This happens through inhibiting certain serine/glycine synthesis enzymes (for a more detailed visualization, see Figure 1C).

Cancers are known to differ from ‘usual’ energy production, shown by for example the Warburg Effect (Asare-Werehene et al., 2014). Several cancer subtypes produce their own serine and glycine via intracellular synthesis, and as a result become dependent and ‘addicted’ to this form of energy production (Geeraerts et al., 2021). Through indirectly inhibiting serine/glycine, these SSRIs cause serine-glycine dependent tumors to have less energy production, inhibiting cancer growth as a result. In addition, sertraline’s anti-proliferative activity is further enhanced by mitochondrial inhibitors. Furthermore, Kannen et al. (2011) showed that Fluoxetine could have an oncostatic (cancer inhibiting) effect on carcinogenic tissue in colon cancer.

Figure 1A

5-HT production and spread in the CNS

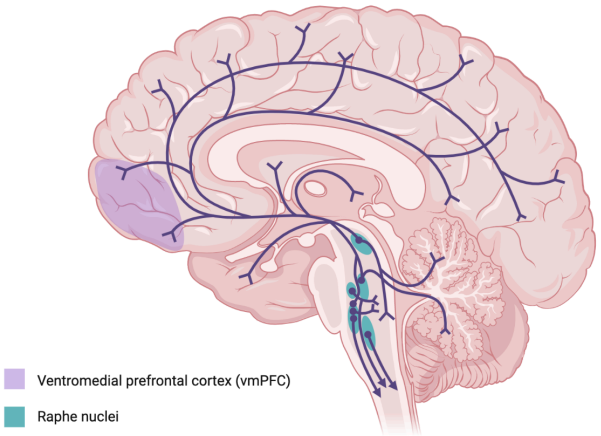

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Figure 1B

The chemical synthesis of 5-HT

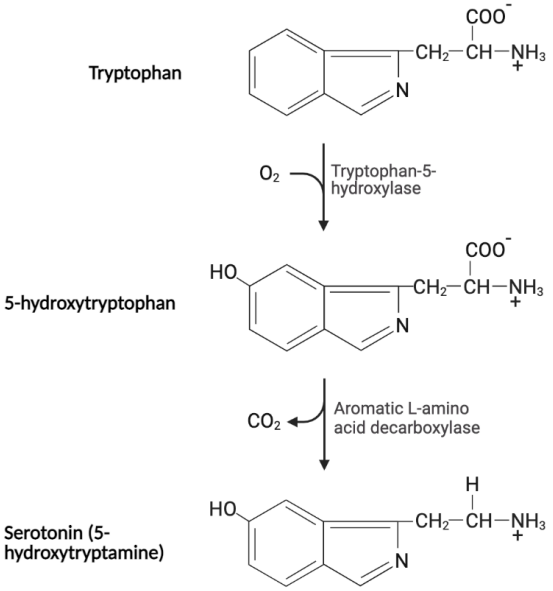

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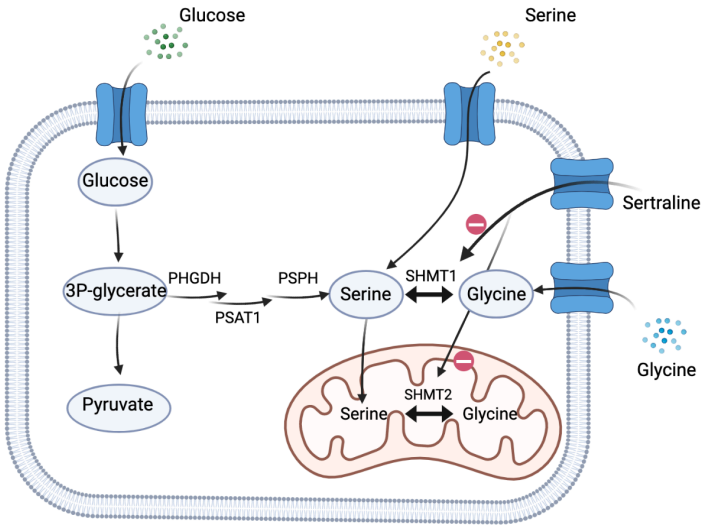
Figure 1C

Sertraline's effect on Serine & Glycine through SHMT inhibition



Note. The SSRI Sertraline targets the serine/glycine synthesis enzyme called serine hydroxymethyltransferase (SHMT1 & SHMT2), causing serine/glycine synthesis to decrease. PHGDH: phosphoglycerate dehydrogenase; PSAT1: phosphoserine aminotransferase; PSPH: phosphoserine phosphatase.

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Moorman et al. (2005) did not find any negative effects of SSRI usage in ovarian cancer, and Xu et al. (2006) found a decreased risk of colorectal cancer associated with daily SSRI usage. These are just a few examples of promising research into ADs and inhibition of cancer cells.

As discussed, ADs seem to modulate certain growth aspects in different types of cancer growth, mostly through effects of GDS. But what about tumors in the CNS? Liu et al. (2014) showed that the SSRI Fluoxetine could even suppress glioblastoma (GBM), one of the most common and most treatment-resistant malignant brain tumors (*About Glioblastoma*, 2022; Ohgaki & Kleihues, 2007; Maher et al., 2001). Ohgaki & Kleihues (2007) similarly showed that this SSRI could cause Calcium (Ca^{2+}) levels to drastically increase in the mitochondria of glioma cells, triggering apoptosis. These briefly discussed studies show the intriguing biological possibilities of AD use in cancer patients, and evidence for brain cancer patients seems to be growing too.

Although ADs seem an intriguing avenue for oncology research, what about the other side of the coin? These older studies are countered by a number of more recent studies, stating that various ADs were not a concern in breast cancer patients (Stapel et al., 2021; Ashbury et al., 2010; Wernli et al., 2009; Coogan et al., 2009, 2008; Tamim et al., 2006). Another large-scale linkage study in Finland showed no clear harmful or beneficial association between AD usage and cancer (Haukka et al., 2009). Multiple studies have found that TCA usage can also have an oncostatic effect (Walker et al., 2010; Daley et al., 2005; Xia et al., 1999). An important point to note is that most if not all studies relating to cancer use a significantly higher AD dose than is normally prescribed for psychological problems. Overall results show that modern ADs show promising effects in cancer patients, and it is only the older (and rarely used) types of ADs that seem to have negative effects (Sharpe et al., 2002; Iishi et al., 1993; Brandes et al., 1992; van Schaik & Graf, 1991). But if depression, a mood disorder shown to have negative cognitive effects (Murrough et al., 2011), can often be comorbid with brain cancer, then how will AD usage affect cognition in these patients?

Antidepressants and Cognition

These varying results therefore raise a different question; what about cognitive outcome in these patients? Patients that received ADs can suffer from a number of problems. As discussed before, ADs are most often prescribed for Depression, Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD), Panic disorder, severe phobias, bulimia, and PTSD (NHS website, 2022). These disorders are all associated with the risk of worse cognitive performance (Schuitevoerder et al., 2013; McDermott & Ebmeier, 2009; Eysenck et al., 2007; Rabins et al., 1984). A systematic review on AD use in controls without a psychiatric diagnosis (Knorr et al., 2019) showed these drugs to have a negative effect on cognition such as decreased divided- and sustained attention, hostility, and sleep quality. It also showed increased activity in the amygdala in relation to happy faces.

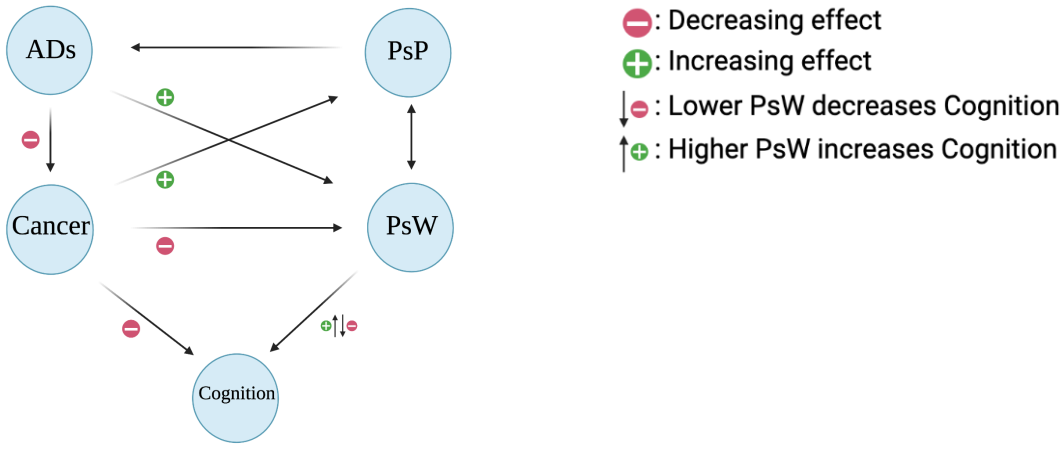
Cancer and Cognition

Research shows that brain tumors and its various treatments have a negative impact on cognitive performance (Zucchella et al., 2013; Taphoorn & Klein, 2004).Various treatments, like radiotherapy, chemotherapy, immunotherapy, and surgery are all linked to poorer cognition in cancer patients as well (Joly et al., 2020; Durand et al., 2015; Noad et al., 2004). This makes brain cancer patients to be a risk group when it comes to cognitive decline, and is therefore a very relevant group to be studied further. Cranial radiotherapy has also been associated with brain damage like severe demyelination (Borges et al., 2021) which can indirectly lead to cognitive decline and memory-related problems. (Turnquist et al., 2020; Makale et al., 2016). In this context, an extensively studied phenomenon is that of ‘chemo brain’, also called cancer-related cognitive impairment or CRCI (Hermelink, 2015; Janelsins et al., 2014). The main complaints of chemo brain are lapses in concentration, attention, memory, and experiencing confusion. Different studies report that anywhere from 15-75% of patients experience chemo brain (Janelsins et al., 2014).

Antidepressants, Cancer and Cognition

To summarize, numerous studies seem to point towards positive effects. An amount of studies do not show an effect of ADs on cancer at all, and there is also a large amount of others also show that ADs can have an inhibitory effect on cancer growth. As previously discussed, with a decline in tumor size, relative cognitive improvement would be expected. On the other hand, the psychological problems for which ADs are prescribed are associated with relatively worse cognitive performance compared to people that have no psychological disorder (Schuitevoerder et al., 2013; McDermott & Ebmeier, 2009; Eysenck et al., 2007; Rabins et al., 1984). This raises the following question: If ADs do inhibit tumor growth, will the resulting cognitive improvement outweigh the cognitive problems linked to AD associated problems (e.g. depression)? To visualize the proposed interactions between these variables, the Antidepressant Psycho-Oncological Interaction Model (APO-IM) is proposed in Figure 2.

Figure 2.



Note. The proposed Antidepressant Psycho-Oncological Interaction Model (APO-IM).

PsP: Psychological Problem(s). PsW: Psychological Wellbeing. Cancer has a decreasing effect on PsW and Cognition, and an increasing effect on PsP. A lower PsW increases PsP. With certain PsP, antidepressants (ADs) are prescribed. ADs are shown to have an oncostatic effect, and a positive effect on PsW. Higher PsW increases Cognition; lower PsW decreases Cognition. The APO-IM is constructed under the assumption that ADs inhibit cancer growth.

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Research Questions & Hypotheses

The present study will conduct research on the effect of the use of ADs in patients with a brain tumor, and the cognitive outcome of people taking ADs relative to those that do not take ADs. This study will ask the question whether anti-depressants will have an effect on patient survival rate in brain cancer patients, and the hypothesis is that AD use will have a positive effect on patient survival rate. Furthermore, this study will pose the question whether ADs have an effect on cognitive performance in brain cancer patients. The hypothesis will be that there will be a positive effect on cognitive performance. Lastly, this study will look at the effect of AD usage on brain tumour size in brain cancer patients. The hypothesis will state that there will be a positive (oncostatic) effect from ADs on tumour size.

Methods

Participants

This study consisted of 74 brain cancer patients undergoing resection surgery at the Elizabeth TweeSteden Hospital in Tilburg, The Netherlands. 18 patients reported to be male, and 56 reported to be female. The participants had ages ranging from 36 to 81 years old. (M = 56.02, SD = 11.07). Patients were divided into two equally sized groups (AD group & control group) of 37 patients. One group was selected on the use of anti-depressants, and an equal amount of patients not taking anti-depressants were matched to serve as a control group. The two groups were matched for age, sex, education (M = 4.86, SD = 1.162), and cancer subtype (Meningioma, High-Grade Glioma, Low-Grade Glioma). Education level was split into groups using the Verhage Education Level (Verhage, 1964). Glioma grading was performed using the WHO-classification (Grade I-II classed as Low-Grade, Grade III-IV classed as High-Grade)(WHO website, 2023; Louis et al., 2021). Patient survival/death was recorded, and the difference between groups was compared over time.

ADs were analyzed as a single group because of a restricted sample size[1]. Exclusion criteria were an age under 18, progressive neurological disease, psychiatric/acute neurological disorder within the past 2 years, previous intracranial surgery, and/or reduced testability (e.g. lack of Dutch proficiency, or estimated IQ < 85). Two patients were excluded from the study; one patient needed another surgery, and another patient was excluded due to a language barrier during testing. All patients provided written informed consent. All data used in this study were anonymously processed. For an overview of sample characteristics, see Appendix A.

Materials and Procedure

Demographic & Clinical Research Data

Data were gathered from patients between November 2010 and August 2017, at Tilburg's Elizabeth TweeSteden Hospital (ETH) in The Netherlands. Here, patients are neuropsychologically assessed as a standard part of the internal clinical care, one day prior to resection surgery (T0). They are then also followed up after three months (T3), for neuropsychological assessment (NPA) again. Participating patients had neuropsychological assessment and an MRI at T0, T3, and T12. All patients received clinical follow-up at either the Elizabeth TweeSteden Hospital or the Catharina Hospital in Eindhoven, The Netherlands. Demographic patient information was collected through the use of a semi-structured interview at T0, and relevant clinical patient information was gathered through digital patient charts.

[1] Data on the type of AD that were taken was selectively reported.

Clinical Imaging

Patients were followed up at three months (T3) and twelve months (T12) with MRI-scans. These MRI-scans were used to determine the WHO-grade. The T0 MRI scan was used to assess maximum Primary Tumor diameter expressed in cm (PT⌀), and maximum Primary Tumor Volume (PTV), expressed in cm^3. The baseline scans were the first post-operative scans, done ≤ 48 h after surgery. PT⌀ and PTV were measured through tumor delineation, using an MRI scan set one day before tumor resection.

Survival Rate

Survival rate was recorded between each timeframe (T0-T3, T3-T12, T0-T12) where Group Survival Rate (GSR) was calculated in percents, with Patient Death (PD) over Total Patients (TP).

$$GSR = \frac{PD}{TP} * 100$$

This way, a difference between Group Survival Rate (GSR) can be assessed between groups in regards to frequency. Alive patients were set at 1, and deceased patients set at 0- a binary score.

Neuropsychological Assessment

Patients had cognitive screening at T0, set to 1 day before the resection surgery, and followed up with identical cognitive testing at T3 and T12. All neuropsychological tests were administered by a trained test administrator. Patients sat down in front of a notebook computer for cognitive testing for the duration of 30-40 minutes, before being asked to participate in two additional pencil-and-paper tasks for the duration of approximately 5 minutes.

Cognitive testing consisted of the Dutch translation of the CNS Vital Signs (CNSVS), a computerized test battery consisting of 7 well-known tasks testing various cognitive functions.

These tests consist of a Verbal- and Visual Memory Test, the Finger Tapping Task, Symbol Digit Coding, the Stroop Test, the Shifting Attention Task, and the Continuous Performance Task (Gualtieri et al., 2006). In addition to the CNSVS test battery, two paper-and-pencil tests were administered; the Digit Span and the Fluency test. This way, an extensive overview of cognition and its course over time could be created in the form of cognitive test results. For a summary of every administered test, see Appendix B.

Statistical Analyses

Statistical analyses were performed using SPSS. The Kolmogorov-Smirnov Test was used to assess normal distribution for cognitive test results per test, education level, PT⌀ and PTV to control for test validity with assumed normal distribution. Cognitive test results at T0 were averaged per test across both the groups at T0, T3 and T12 using descriptive statistics, and compared between groups using an Independent Samples T-test at each of the three timepoints. Changes in cognitive test results over time were assessed using a Repeated Measures ANOVA for both groups separately. The Bonferroni Correction was applied to correct for multiple testing (2 groups x 15 tests, p=0.05/30, setting p-value at .00167). Changes over time were measured between timeframes T0-T3, T3-T12, and total time T0-T12. At time intervals T0, T3, and T12, the cognitive test results were averaged across patients in both groups. Survival rate was assessed over time using a Repeated Measures ANOVA. These changes over time were calculated between timeframes T0-T3, T3-T12, and total time T0-T12. Survival rate was calculated in percentages per group. Differences between the two groups were compared at each time interval using an Independent Samples T-test. PT⌀ and PTV were averaged for groups and compared between groups using an Chi-Square test. Statistics were performed using SPSS.

Results

Group Survival Rate

GSR in timeframe T0-T3

In the control group, a total of 0 patients passed away during the 3-month period, where GSR = 100%. In the AD group, a total of 2 patients passed away over the 3-month period, where GSR = 95%. A Chi-Square test found no significant difference in group survival rate (X^2 (1, N = 72) = 0.0282, p = .8867). In total, 2 patients passed away over the 3-month period, where GSR=97%.

GSR in timeframe T3-T12

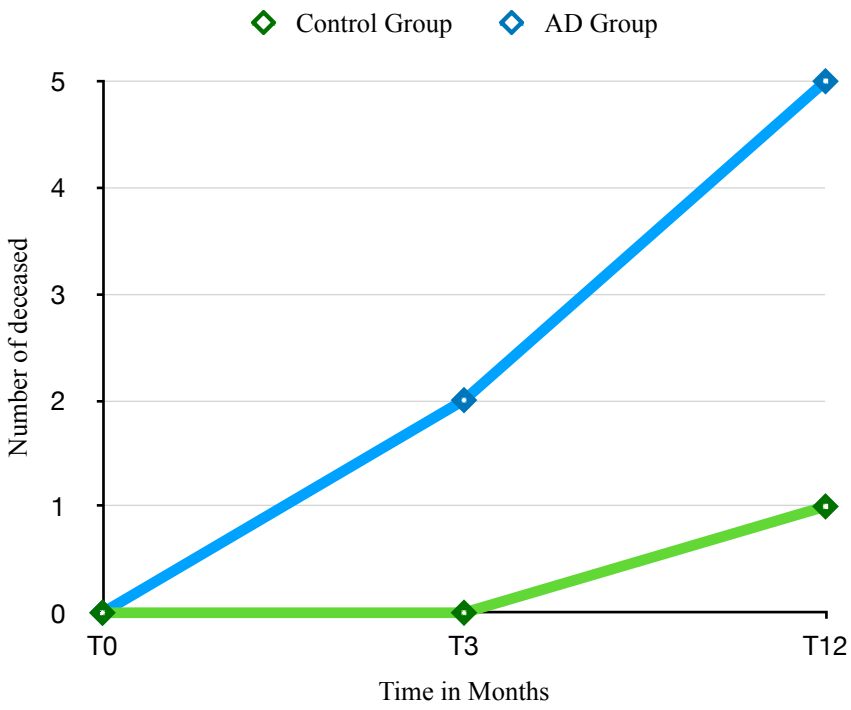
In the control group, a total of 1 patient passed away during this 9-month period, where GSR = 97%. In the AD group, a total of 3 patients passed away over this 9-month period, where GSR = 92%. A Chi-Square test found no significant difference in group survival rate (X^2 (1, N = 72) = 0.0338, p = .8542). In total, 4 patients passed away over this 9-month period, where GSR=95%.

Cumulative GSR in total timeframe T0-T12

In the control group, a total of 1 patient passed away during the full 12-month period, where GSR = 97%. In the AD group, a total of 5 patients passed away over the full 12-month period, where GSR = 86%. A Chi-Square test found no significant difference in group survival rate (X^2 (1, N = 72) = 0.1227, p = .7261). In total, 6 patients passed away over the 12-month period, where GSR=92%. No significant differences in survival rate between the control group and the AD group were found, meaning there is no significant effect of antidepressant use on patients' survival rate. For a visualisation of the relationship between time and number of deceased patients, see Figure 3.

Figure 3.

Number of deceased patients over time.



Note. This figure shows the number of deceased at each of the three measuring points (T0, T3, T12). There are no significant differences between the two groups (N_{AD}=37, $N_{Control}$=37).

Cognitive Performance

Cognitive testing consisted of the Dutch translation of the CNS Vital Signs (CNSVS). Test results were standardized and compared between groups on each timeframe. The change in performance within groups was also calculated over time. See Table 6, Table 7 and Table 8 for the cognitive performance results between groups in measurements T0, T3 and T12 respectively. See Table 9 for the change in performance over time within groups.

Table 6.

Independent Samples t-tests at T0 between control group and AD group test results

T0		Control Group	AD Group	t-value	p-value
Visual Memory Score	M SD	42.39 5.82	43.79 5.48	t(68)=1.035	.3044
Verbal Memory Score	M SD	49.90 6.40	48.29 5.93	t(67)=3.903	.0002*
Memory Domain Score	M SD	46.15 6.11	46.04 5.71	t(67)=0.077	.9388
Processing Speed	M SD	42.76 17.27	42.11 16.58	t(70)=0.163	.8712
Motor Speed	M SD	105.78 24.83	108.83 17.11	t(70)=0.604	.5481
Psychomotor Speed	M SD	74.27 21.05	75.47 16.85	t(70)=0.267	.7902
Executive Functioning	M SD	28.92 27.99	34.32 20.60	t(65)=2.365	.0210*
CPT Reaction Time	M SD	428.22 40.44	442.39 61.50	t(68)=1.151	.2539
Stroop I Reaction Time	M SD	332.57 104.99	329.48 114.46	t(66)=0.116	.9079
Stroop I Interference	M SD	1.49 0.66	1.54 0.49	t(68)=0.358	.7213
Stroop II Reaction Time	M SD	697.81 174.37	696.53 212.53	t(68)=0.027	.9781
Digit Span Forward	M SD	8.20 2.86	8.50 1.90	t(18)=0.276	.7855
Digit Span Backward	M SD	6.20 2.39	5.90 2.42	t(18)=0.279	.7835
Fluency Task Percentile Score	M SD	34.69 29.13	33.48 25.60	t(47)=0.1535	.8786
Fluency Task Predicted Score**	M SD	37.03 3.22	44.30 8.00	t(58)=4.941	.0001*

Note.
*Significant ($p<0.05$) difference between control group and AD group.
**Predicted scores based on education level.

T0 Test Results

Independent Samples T-tests showed significant differences in verbal memory score, executive functioning, and predicted score in the fluency task at T0. The other tests did not show any significant differences. In the Verbal Memory Score, the control group scored significantly higher ($t(67)=3.903$, $p=.0002$) than the AD group. On the other hand, the AD group scored significantly higher ($t(65)=2.365$, $p=.0210$) than the control group on executive functioning at T0, but this was negated by Bonferroni Correction ($p >.00167$). The fluency task predicted score was significantly higher for the AD group, but the actual fluency task percentile score showed no significant difference.

Table 7.

Independent Samples t-tests at T3 between control group and AD group test results

T3		Control Group	AD Group	t-value	p-value
Visual Memory Score	M SD	42.47 4.85	41.54 6.18	t(54)=0.630	.5311
Verbal Memory Score	M SD	49.17 5.04	46.59 6.07	t(55)=1.752	.0853
Memory Domain Score	M SD	45.82 4.95	44.07 6.13	t(54)=1.175	.2450
Processing Speed	M SD	49.38 18.90	40.61 17.71	t(55)=1.806	.0763
Motor Speed	M SD	109.60 25.40	105.03 13.62	t(57)=0. 857	.3951
Psychomotor Speed	M SD	79.49 22.15	72.82 15.67	t(55)=1.308	.1962
Executive Functioning	M SD	33.15 25.59	32.85 20.07	t(52)=0.048	.9620
CPT Reaction Time	M SD	441.69 54.07	466.29 63.90	t(55)=1.571	.1219
Stroop I Reaction Time	M SD	343.38 119.28	366.62 108.88	t(56)=0.775	.4416
Stroop I Interference	M SD	1.48 0.63	1.40 0.55	t(57)=0.519	.6059
Stroop II Reaction Time	M SD	No data			
Digit Span Forward	M SD	8.44 2.13	8.42 2.61	t(19)=0.019	.9852
Digit Span Backward	M SD	5.89 1.76	5.83 2.98	t(19)=0.054	.9578
Fluency Task Percentile Score	M SD	41.32 32.50	40.27 26.40	t(45)=0.121	.9046
Fluency Task Predicted Score**	M SD	37.03 3.22	37.30 2.59	t(72)=0.397	.6922

Note.
*Significant ($p<0.05$) difference between control group and AD group.
**Predicted scores based on education level.

T3 Test Results

Independent Samples t-test results at T3 did not show any significant differences between groups. Stroop II was not included due to a lack of valid data for this task at T3.

Table 8.

Independent Samples t-tests at T12 between control group and AD group test results

T12		Control Group	AD Group	t-value	p-value
Visual Memory Score	M SD	43.00 5.68	42.60 4.20	t(24)=0.192	.8496
Verbal Memory Score	M SD	50.27 5.89	45.30 5.77	t(23)=2.083	.0485*
Memory Domain Score	M SD	46.64 5.79	43.95 4.99	t(23)=1.239	.2277
Processing Speed	M SD	49.50 13.77	43.30 19.45	t(24)=0.953	.3500
Motor Speed	M SD	115.35 17.10	104.90 21.37	t(25)=1.399	.1742
Psychomotor Speed	M SD	82.43 15.44	74.10 20.41	t(24)=1.184	.2482
Executive Functioning	M SD	44.13 14.39	35.50 23.99	t(24)=1.152	.2606
CPT Reaction Time	M SD	428.00 45.72	469.40 62.06	t(25)=1.990	.0576
Stroop I Reaction Time	M SD	763.65 170.38	776.10 121.54	t(25)=0.202	.8415
Stroop I Interference	M SD	1.49 0.67	1.47 0.67	t(25)=0.075	.9409
Stroop II Reaction Time	M SD	No data			
Digit Span Forward	M SD	7.67 2.52	8.67 3.79	t(4)=0.381	.7229
Digit Span Backward	M SD	5.67 1.53	6.67 2.89	t(4)=0.530	.6244
Fluency Task Percentile Score	M SD	34.67 24.56	53.00 37.24	t(17)=1.250	.2281
Fluency Task Predicted Score**	M SD	37.03 3.22	37.30 2.59	t(72)=0.397	.6922

Note.
*Significant ($p<0.05$) difference between control group and AD group.
**Average Predicted Scores based on education level.

T12 Test Results

Independent Samples T-tests showed significant differences in verbal memory score at T12. The other tests did not show any significant differences. In the verbal memory score, the control group scored significantly higher ($t(23)=2.083$, $p=.0485$) than the AD group, but this result was negated by the Bonferroni Correction ($p >.00167$).

Table 9.

Cognitive performance over time

		F	df	p-value	Change score
Visual Memory Score					
Control Group	T0-T3	0.200	1	.658	0.08
	T0-T12	0.950	2	.401	0.61
AD Group	T0-T3	3.114	1	.090	2.25
	T0-T12	0.288	2	.753	1.19
Verbal Memory Score					
Control Group	T0-T3	0.099	1	.755	0.73
	T0-T12	0.219	2	.805	0.37
AD Group	T0-T3	5.232	1	.031*	1.70
	T0-T12	0.056	2	.945	2.99
Memory Domain Score					
Control Group	T0-T3	0.008	1	.929	0.33
	T0-T12	0.234	2	.794	0.49
AD Group					
	T0-T3	7.890	1	.010*	1.97
	T0-T12	0.258	2	.776	2.09
Processing Speed					
Control Group	T0-T3	5.806	1	.023*	6.62
	T0-T12	2.428	2	.110	6.74
AD Group	T0-T3	0.246	1	.624	1.50
	T0-T12	1.608	2	.288	1.19
Motor Speed					
Control Group	T0-T3	0.642	1	.430	3.82
	T0-T12	1.519	1.297**	.240	9.57
AD Group	T0-T3	5.684	1	.024*	3.80
	T0-T12	0.213	1.272**	.711	3.93
Psychomotor Speed					
Control Group	T0-T3	3.080	1	.091	5.22
	T0-T12	2.150	1.342**	.161	8.16
AD Group	T0-T3	3.639	1	.068	2.65
	T0-T12	0.028	1.293**	.920	1.37
Executive Functioning					
Control Group	T0-T3	0.717	1	.405	4.23
	T0-T12	2.302	2	.122	14.21
AD Group	T0-T3	0.773	1	.388	34.32
	T0-T12	0.353	2	.708	35.50
CPT Reaction Time					
Control Group	T0-T3	2.919	1	.099	13.47
	T0-T12	0.384	2	.685	0.22
AD Group	T0-T3	7.519	1	.011*	23.90
	T0-T12	0.682	2	518	27.01
Stroop I Reaction Time					
Control Group	T0-T3	0.135	1	.716	10.81
	T0-T12	0.551	2	.541	431.08
AD Group	T0-T3	4.848	1	.037*	37.14
	T0-T12	0.204	2	.818	446.61
Stroop I Interference					
Control Group	T0-T3	0.294	1	.592	0.01
	T0-T12	0.798	1.257**	.411	0.00
AD Group	T0-T3	1.542	1	.225	0.14
	T0-T12	0.485	2	.623	0.07
Digit Span Forward					
Control Group	T0-T3	1.224	1	.305	0.24
	T0-T12	3.500	2	.132	0.53
AD Group	T0-T3	1.818	1	.214	0.08
	T0-T12	0.333	2	.750	0.17
Digit Span Backward					
Control Group	T0-T3	0.412	1	.542	0.31
	T0-T12	0.560	2	.610	0.53
AD Group	T0-T3	1.563	1	.247	0.07
	T0-T12	1.000	2	.500	0.77
Fluency Task Percentile Score					
Control Group	T0-T3	0.064	1	.803	6.63
	T0-T12	0.511	2	.612	0.02
AD Group	T0-T3	0.790	1	.387	6.79
	T0-T12	4.387	2	.052	19.52

Note.
*Significant ($p<0.05$) difference between control group and AD group.
**Sphericity assumption violated; Greenhouse-Geisser values reported.

Cognitive Test Performance over time

Performance over time was measured within groups to look for an effect over time. Significant decreases in performance were found in various tests over 3-month timeframe T0-T3, but no significant changes over time were reported for the 12-month timeframe T0-T12.

Various significant effect were found on timeframe T0-T3. This consisted of a significant decrease in verbal memory scores at T0-T3 ($F(1,55)=5.232$, $p=.031$). There was also a significant decrease in memory domain score in the AD group at T0-T3 ($F(1,54)=7.890$, $p=.010$). There was a significant decrease in processing speed in the control group at T0-T3 ($F(1,24)=5.806$, $p=.023$). Then there was a significant decrease in motor speed in the AD group at T0-T3 ($F(1,57)=5.684$, $p=.024$). There was also a significant negative effect on CPT reaction time in the AD group at T0-T3 ($F(1,55)=7.519$, $p=.011$). Lastly there was a significant negative effect on response time in Stroop-I in the AD group at T0-T3 ($F(1,56)=4.848$, $p=.037$). All of these effects disappeared in the long timeframe T0-T12, though. In summary, a number of significant effects of time on cognitive performance were found on timeframe T0-T3, but all effects disappeared on timeframe T0-T12.

Max Primary Tumor Diameter and Volume

Max Primary Tumor Diameter (PT⌀) was compared between the control group ($M=4.78$, $SD=14.37$) and the AD group ($M=4.08$, $SD=1.30$). At T0, no significant difference was found between the two groups ($t(72)=0.307$, $p=.7593$) in max primary tumor diameter.

Data on Max Primary Tumor Volume (PTV) were available selectively; for sample sizes and ranges, see Appendix A. PTV values were compared at T0 between the control group ($M=36.91$, $SD=28.60$) and the AD group ($M=23.34$, $SD=18.69$). No significant difference in volume was found between the two groups ($t(10)=0.756$, $p=.4669$). This means that at T0, there was no significant differences between the tumor volume in the control- and AD group.

Discussion

The current study has attempted to look into the effects of antidepressants on tumor size and cognition in brain cancer patients. Data shows some significant results in cognitive changes throughout testing, but all of these significant changes only show over the initial three-month period, and all effects faded over a twelve-month period. Change over time significantly differed between the Control- and AD Group at timeframe T0-T3, where the AD group seemed to perform relatively worse. However, across the timeframe of the entire study (T0-T12) most of these significant effects disappeared. This means that over the twelve-month period, there were almost no significant differences between the two groups.

Differences in tumor volume and tumor diameter were both not statistically significant between the two groups at baseline. Given that tumor sizes did not differ between the two groups at baseline, but cognitive performance did decline in the AD group, one could hypothesize that AD can have a negative effect on cognition throughout the treatment course. However, we cannot rule out if changes in tumor volume were related to AD use. The current study therefore shows no significant effects of antidepressant usage on either tumor volume or tumor diameter. This study also found no significant difference between tumor sizes. As antidepressant use is associated with worse cognitive performance, this could possibly negate their oncostatic effect, and therefore show no change in cognitive performance. Further research needs to be done to find more evidence of the oncostatic effect of SSRI usage, and future research needs to delve deeper into cognitive performance where possible.

Limitations

Important to note is that there are factors that could not be taken into account, due to restricted sample size and/or lack of data. These factors include duration of medication use before the study, combination of different medications and their possible side-effects, and therapy form (e.g. radiotherapy, chemotherapy). Another factor that could not be taken into account was disease progression, due to restricted sample size. These could be relevant factors to include in future studies because these factors could (in)directly influence the patients' physical and mental health, and as a result possibly alter cognitive performance. Another limitation of the current study is that a variety of SSRIs were combined in the AD group. The present study is also constrained by a fairly limited sample size and a single instance of non-normal distribution in cognitive testing. Although t-tests are generally resistant to violations of normal distribution, this may not hold true for smaller samples (in this study, both groups had $N = 37$, where small sample size is considered $N < 50$).

Evidence of SSRI usage and cancer inhibition varies between different subtypes of SSRIs, and also between other types of ADs. The various ADs could not be researched independently due to a restricted sample size. Researching the seemingly promising SSRIs, e.g. fluoxetine (Liu et al. 2014, Kannen et al., 2011, Ohgaki & Kleihues, 2007) might yield more promising results. Another important factor to note is that antidepressants are usually prescribed for mood disorders, which exist on a spectrum (Benvenuti et al., 2015). This can cause sampling bias, as it is likely that only patients that are on the less severe end of the mood disorder spectrum will agree to be a part of the study. This can possibly alter the outcome of the study. For the future, it could be important to map the severity and the type of mood disorder in a detailed manner.

Future directions

Having larger sample sizes could produce a more dependable dataset, lowering possibility of errors, and even leading to different results or conclusions. Specifically using populations selected on antidepressant usage and screening for various relevant variables could prove to be a more effective way of conducting research on the effect of these SSRIs on tumors. Future studies could focus on using only one SSRI (e.g. fluoxetine) to better isolate possible effects of these medications on tumor growth, yielding more dependable results.

Conclusion

In summary, this study's results are inconclusive about whether antidepressants are an applicable form of medication when it comes to brain tumors. However, this study shows that when SSRIs are generalized and not studied as separate entities, results dissipate. Several referenced studies that focus on only one type of SSRI do show intriguing results, and these types of research setups should be explored more thoroughly to fully understand the mechanisms at hand. Although referenced studies do show promising results when it comes to peripheral tumors, this study was unable to replicate the results in a setting where only brain tumors are researched. Future studies will need to shed more light on the complicated and yet intriguing interaction between carcinogenesis and antidepressants. For now, it remains an interesting and promising topic for future research to dive into.

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Appendix A

Sample Group Characteristics

Characteristic	AD Group N = 37	Control Group N = 37	Total Sample N = 74
Sex			
Male	9 (24.3%)	9 (24.3%)	18 (24.3%)
Female	28 (75.7%)	28 (75.7%)	56 (75.7%)
Age in years			
M	57.03	55.03	56.02
SD	10.75	11.43	11.07
Range	38-79	36-81	36 - 81
Education Level*			
Low	10 (27.0%)	13 (35.1%)	23 (31.1%)
Middle	18 (48.7%)	10 (27.0%)	28 (37.8%)
High	9 (24.3%)	14 (37.9%)	23 (31.1%)
Disease Diagnosis			
High-Grade Glioma (HGG)	11 (29.7%)	8 (21.6%)	19 (29.7%)
Low-Grade Glioma (LGG)	4 (10.8%)	5 (13.5%)	9 (10.8%)
Meningioma (MEN)	22 (59.5%)	24 (64.9%)	46 (59.5%)
Death Rates over time**			
T0-T3	2	0	2
T3-12	3	1	4
T0-12	5	1	6
Max Primary Tumor Diameter (PT⌀) in cm			
M	4.08	4.78	4.41
SD	1.30	14.37	1.39
Range	1.66 - 5.94	25.6 - 86.1	1.66 - 8.61
Max Primary Tumor Volume (PTV) in cm^3***	*N = 3*	*N = 9*	*N = 12*
M	23.34	36.91	33.52
SD	18.69	28.60	26.39
Range	1.99 - 36.75	10.08 - 106.13	1.99 - 106.13

Note.

*Education Level classed according to the Verhage Education Level (1-4 = Low, 5 = Middle, 6-7 = High)

**Death Rates per time interval, with numbers showing deceased patients within each time interval.

***Data selectively available; Sample size shown separately. Data did not significantly differ from any group characteristics.

Appendix B

Contents of the CNS Vital Signs

Verbal- and Visual Memory

The Verbal Memory Test (VBM) and Visual Memory Test (VIM) in the CNSVS are adaptations of the Rey Auditory Verbal Learning Test (RAVLT) and the Rey Visual Design Learning Test (RVDLT) respectively. These tests assess verbal- and visual memory. Where the VBM uses words as stimuli, the VIM uses geometric shapes. Fifteen stimuli are presented, one-by-one, onto the computer screen. Every two seconds, a new stimulus is shown. Patients are asked to remember these stimuli. After all fifteen stimuli are presented, the patient is shown a list of thirty stimuli in the same manner, in which the previous fifteen are included in random order. The patient is asked to press the Spacebar when a stimuli from the original list is recognized. At the end of the test battery, a Delayed Recognition trial of both the VBM and VIM are administered. The results of these two tests are summed together to create a memory domain score.

Finger Tapping Task

The Finger Tapping Task (FTT) is a motor sequence learning task, measuring fine motor control, motor speed and visuomotor ability (Mitrushina et al., 1999). In the CNSVS, the FTT consists of the participant tapping the Spacebar as many times as possible in 10 seconds. There is one practice trial, followed by three test trials. The test is done first with the right hand, and then repeated with the left hand.

Symbol Digit Coding

The Symbol Digit Coding (SDC) is a computerized version of the well-known Symbol Digit Modalities Test (SDMT), which consists of linking symbols and numbers and is used to assess psychomotor speed. In the CNSVS, a series of screens is presented, each containing eight symbols at the top of the screen and an according eight boxes below. Patients are asked to type in the number corresponding to the highlighted symbol on the screen, with the key (Figure 4) present during the entire test. For this digital version, the number '1' is excluded to prevent confusion with the lowercase letter 'L'. Patients are asked to do this task as fast as possible, without making errors. This tests lasts 120 seconds. The SDC is scored by counting the number of correct responses within the 120s timeframe. The total of the SDC and the FTT is combined into a composite score of psychomotor speed.

Figure 4.

#	⇒	{	∠	⊗	×	⌜	∩
2	3	4	5	6	7	8	9

Note. The answer key shown in the SDC.

Stroop Test

The Stroop Test is a well-known interference test measuring reaction time, cognitive switching, inhibition and information processing speed. The CNSVS adapted version uses four colors, and four color words. This test consists of three parts. The first part (Stroop-I) consists of color words (RED, YELLOW, GREEN, BLUE) shown on the screen in black. The patient taps on the Spacebar as soon as the word is displayed, to measure reaction time.

The second part (Stroop-II) shows the color words, shown in any of the four colors listed above. The patient is asked to press the Spacebar whenever the color matches the color word. The third part shows the color words, shown in any of the four colors. The patient is asked to press the Spacebar whenever the color does not match the color word. Scores of part two and three are averaged into a score.

Shifting Attention Task

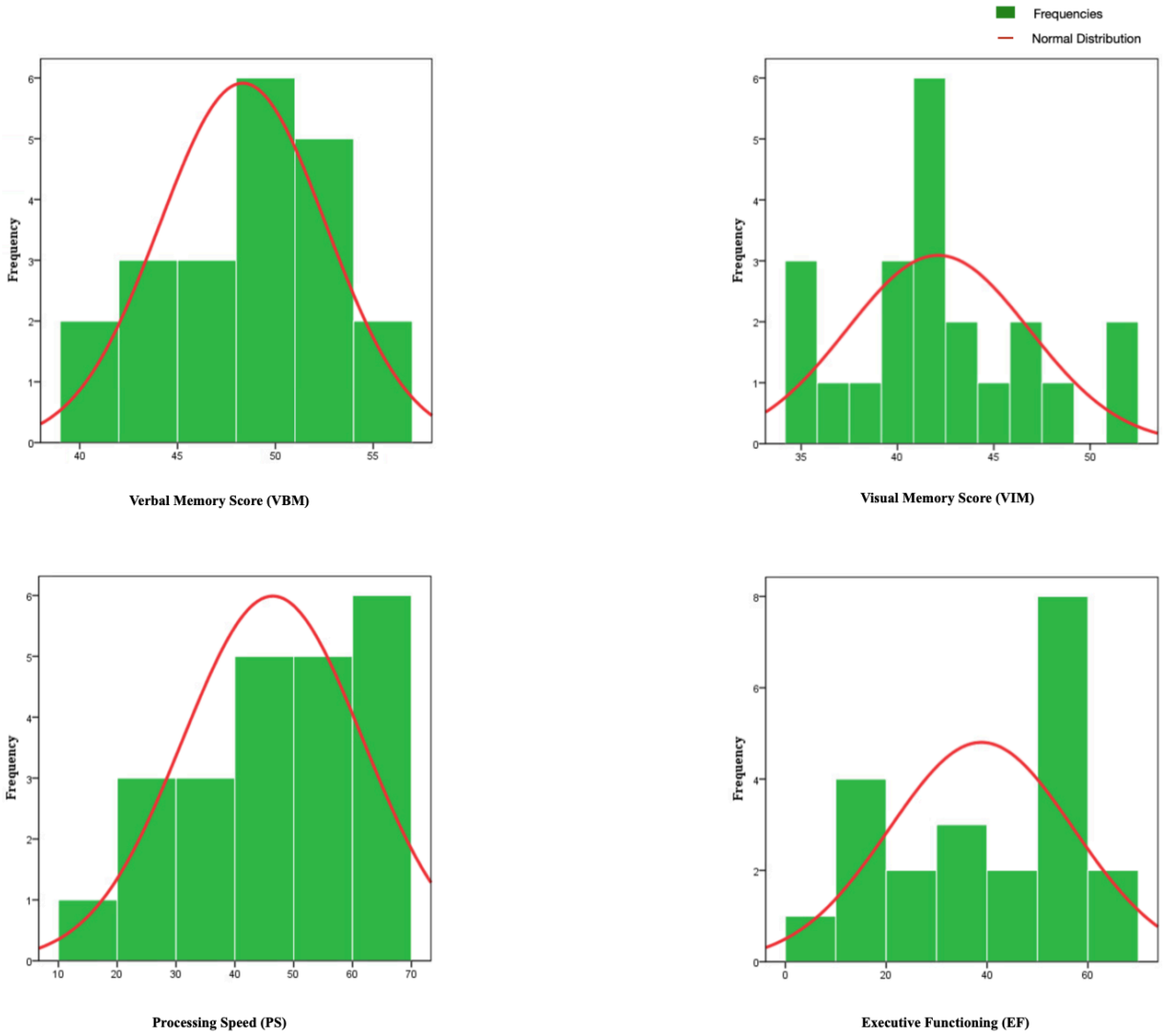
The Shifting Attention Task is (SAT) measures, as the name suggests, the ability to shift the attention between various instructions. Patients are instructed to match geometric shapes, either by size or by color. In the computerized CNSVS version, three shapes appear on the screen. One on the top, and two at the bottom. The top figure will either be a square or a circle, and the bottom two will always be one circle, and one square. All figures are either red or blue, and this is randomly mixed with each trial. The subject is asked to match one of the two bottom shapes to the top shape. There is two possible rules; matching by color or matching by shape. These rules change at random, and this task goes on for 90 seconds. A domain score for cognitive flexibility is assessed based on the correct SAT scores, subtracting the errors in both the SAT and the Stroop Task.

Continuous Performance Test

The Continuous Performance Test (CPT) measures sustained attention. The patient is shown a total of 200 letters in 5 minutes on the screen, and asked to only respond to the letter B by pressing the Spacebar. The letter B will show a total of 40 times, leaving 160 items not to be responded to. A domain score for Complex Attention is calculated by adding up the amount of errors in the Stroop Task, SAT, and CPT (Gualtieri, C. T., & Johnson, L. G. (2006).

Appendix C

Histograms with plotted Normal Distribution for test scores per test



Note. Normal distribution was checked for test validity when normal distribution is assumed. The Kolmogorov-Smirnov test was used to determine the significance of normal distributions.

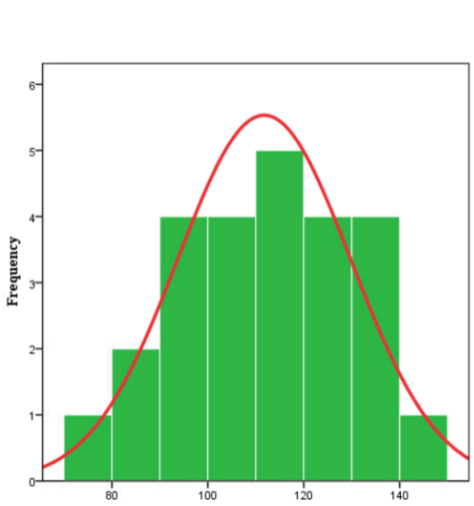
$VBM_M = 48.33$
$VBM_{SD} = 0.93$
$p = .200$

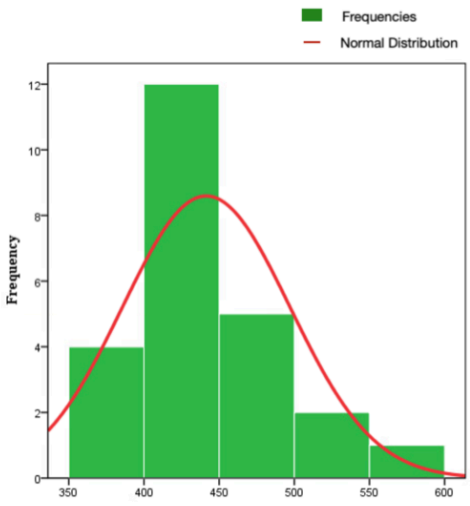
$VIM_M = 42.11$
$VIM_{SD} = 1.01$
$p = .200$

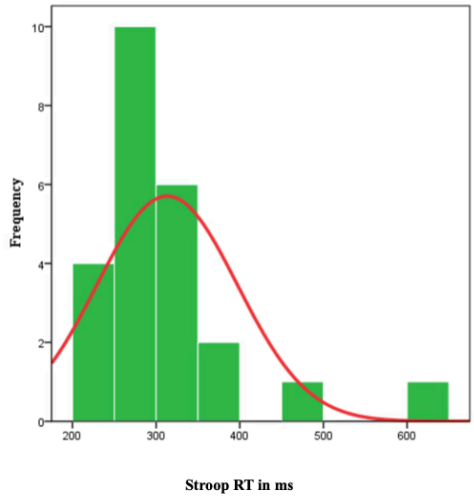
$PS_M = 46.45$
$PS_{SD} = 3.19$
$p = .169$

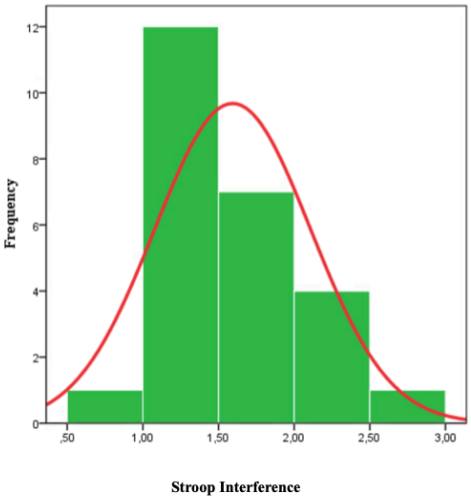
$EF_M = 38.88$
$EF_{SD} = 3.90$
$p = .053$

** = Sig ($p < 0.05$), therefore not normally distributed*









Note. Normal distribution was checked for test validity when normal distribution is assumed. The Kolmogorov-Smirnov test was used to determine the significance of normal distributions.

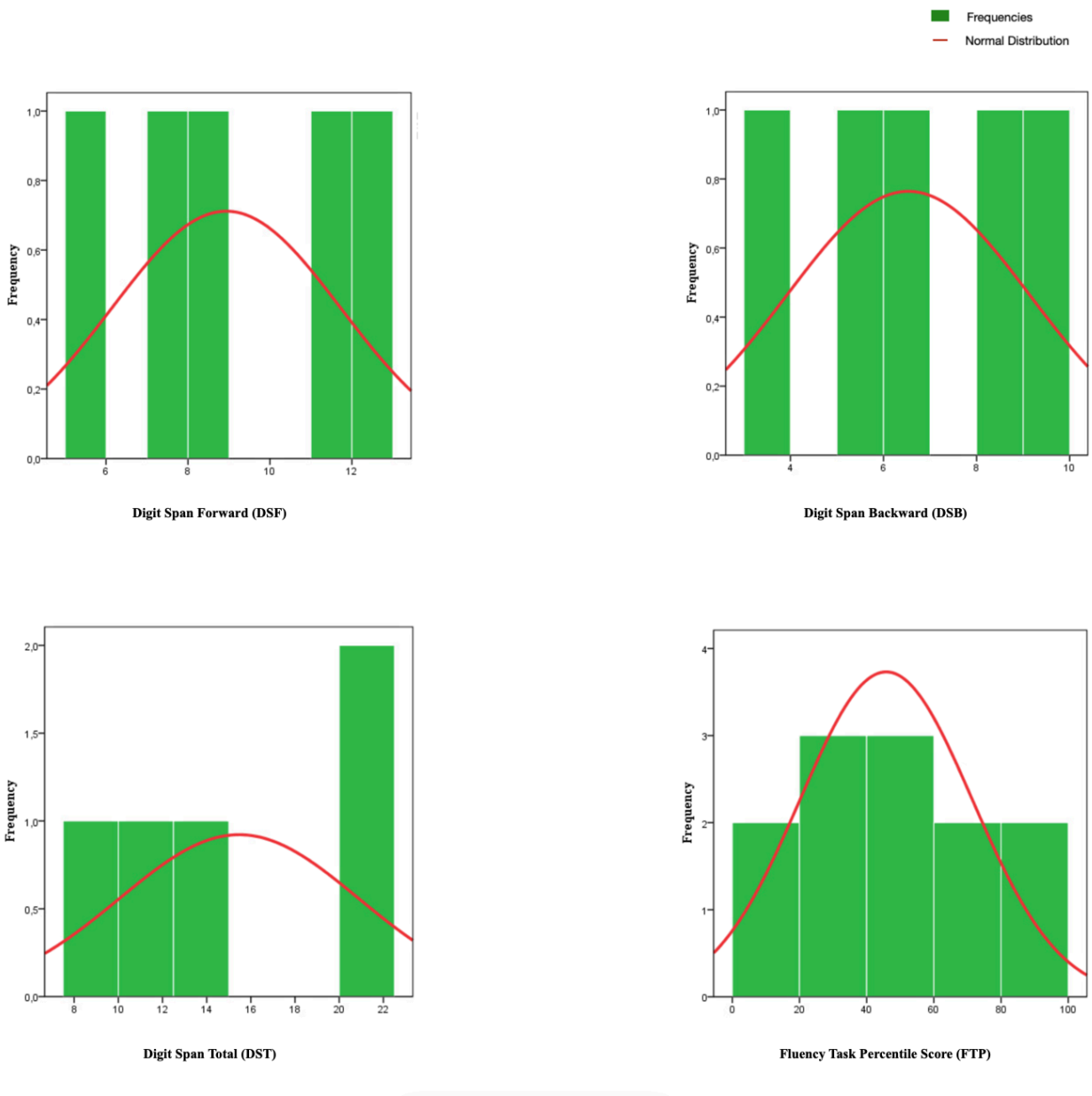
$DSF_M = 8.93$
$DSF_{SD} = 1.25$
$p = .200$

$DSB_M = 6.53$
$DSB_{SD} = 1.17$
$p = .200$

$DST_M = 15.47$
$DST_{SD} = 2.42$
$p = .200$

$FTP_M = 45.81$
$FTP_{SD} = 7.41$
$p = .200$

** = Sig ($p < 0.05$), therefore not normally distributed*



Note. Normal distribution was checked for test validity when normal distribution is assumed. The Kolmogorov-Smirnov test was used to determine the significance of normal distributions.

$MS_M = 111.75$
$MS_{SD} = 3.61$
$p = .200$

$CPT_M = 441.40$
$CPT_{SD} = 11.37$
$p = .073$

$Stroop\text{-}I_M = 313.21$
$Stroop\text{-}I_{SD} = 17.13$
$p = .043$*

$Stroop\text{-}I\text{-}Int_M = 1.59$
$Stroop\text{-}I\text{-}Int_{SD} = 0.10$
$p = .126$

** = Sig ($p < 0.05$), therefore not normally distributed*

Appendix D

Patient dropout

Patient dropout

Patient dropout was reported on each timeframe (T0, T3, T12). Reasons for dropout included invalid test scores, physical/mental incapability, epileptic seizure, unreachability, diagnosed with other cancers, death, rehabilitation, comorbidity, complications, and unwillingness. Patient dropout did not significantly differ between the control Group and the AD group ($t(44)=0.4047$, $p=.6877$). For a summary of patient dropout, see Figure 5.

Figure 5.

Dropout over time per group

	Dropout reason								
Control group	Invalidity	Unable	Unknown	Logistics	Illness	Over max time	No contact	Deceased	Unwilling
T0	1								
T3		1	1	1	1				
T12			4		1	1	1	1	2
AD group	**Total dropout control group = 15**								
T0	1								
T3		1	1	2				2	3
T12		2	3		2	1	1	1	2
	Total dropout AD group = 22								

Note. This figure shows patient dropout at each of the three measuring points (T0, T3, T12). There are no significant differences in dropout rates between the two groups ($N_{AD}=37$, $N_{Control}=37$).

Figure 6.

Visualization of patient dropout over time per group