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Chronic tobacco smoking and neuropsychological impairments: A systematic review and meta-analysis

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Abstract

The link between neuropsychological impairments and chronic tobacco smoking is not clear and in the current literature there is a lack of robust analyses investigating this association. A systematic review of the literature was conducted in order to identify relevant longitudinal and cross-sectional studies conducted from 1946 to 2017. A meta-analysis was performed from 24 studies testing the performance of chronic tobacco smokers compared with non-smokers on neuropsychological tests related to eight different neuropsychological domains. The results revealed a cross-sectional association between neuropsychological impairments and chronic tobacco smoking in *cognitive impulsivity, non-planning impulsivity, attention, intelligence, short term memory, long term memory,* and *cognitive flexibilit*y, with the largest effect size being related to *cognitive impulsivity* (SDM=0.881, p <0.005), and the smallest effect size being related to *intelligence* (SDM=0.164, p<0.05) according to Cohen's benchmark criteria. No association was found between chronic smoking and *motor impulsivity* (SDM=0.105, p=0.248). Future research is needed to investigate further this association by focusing on better methodologies and alternative methods for nicotine administration.

Keywords: *Nicotine, chronic smoking, neuropsychology, impulsivity, memory, intelligence, attention, cognitive flexibility, meta-analysis.*

1.Introduction

Nicotine is a poisonous alkaloid and highly addictive psychoactive substance present in tobacco cigarettes (Benowitz,2009,2010; Mishra et al., 2015; Pontieri et al., 1996; Stolerman & Jarvis, 1995). Cigarettes are the primary form of tobacco consumed globally and are responsible for the death of approximately 6 million people each year worldwide (WHO, 2018). They contain over 4000 chemicals compounds, 43 of those are reported to be carcinogenic, including formaldehyde, cyanide, lead, carbon monoxide, acrolein, and arsenic (Rodgman & Perfetti, 2016; Talhout et al., 2011). The physical effects of chronic smoking are well known. In fact, there is a strong association between chronic tobacco smoking and physical diseases including cardiovascular diseases, respiratory diseases and various forms of cancer (Didkowska et al., 2016; Houghton et al., 2008; Ide et al., 2007; Margaritopoulos et al., 2016; McGrath et al., 2007; Mozaffarian et al., 2016). Direct and indirect exposure to nicotine have been also associated with neurobiological changes (Volkow et al. 2016; Yuan et al., 2015). Particularly, nicotine is reported to increment the number of acetylcholine receptors (nAChR) (Jasinska et al. 2014), which like other drugs, stimulate the release of dopamine in the ventral striatum (Brody et al., 2004; De Biasi & Dani 2011) and produce reinforcing effects that contribute to addiction (Rose, 2006). Nicotine use has been also associated with cognitive modulation, although the evidence for the influence of nicotine on cognition is complex. In fact, while nicotine consumed acutely has been reported to enhance cognition, particularly attention and memory (Heishman et al.2010; Potter & Newhouse, 2007), chronic nicotine use has been linked to cognitive impairments in midlife (Kalmijn 2002; Richards et al. 2003) and to cognitive

deterioration and various types of dementia in old age (Reitz et al., 2007; Sosa-Ortiz et al., 2012; Zhong et al., 2015). Researchers also investigated the co-occurring effects of nicotine use and different types of psychotropic drugs on the neuropsychological and neurobiological processes of individuals, proposing, for example, that nicotine may exacerbate neurological damages in alcohol dependent individuals (Durazzo et al., 2006), and that “opioid and nicotinic-cholinergic neurotransmitters systems interact in important ways to modulate nicotine and opioid effects” (Yoon et al., 2015, p.281). In contrast to the wealth of reviews and meta-analyses in the literature summarising the harmful effects of chronic smoking on individuals’ physical health (e.g. Gandini et al., 2008; Huxley & Woodward, 2011; Jayes et al., 2016; Sasco et al., 2004), the number of reviews investigating the neuropsychological effects of chronic nicotine and tobacco exposure is extremely scarce. In this sense, one of the most relevant examples is the systematic review conducted by Durazzo et al., (2010). According to their findings “chronic smoking is associated with deficiencies in auditory-verbal learning and/or memory, general intellectual abilities, visual search speeds, processing speed, cognitive flexibility, working memory and executive functions, across a wide age range”. (Durazzo et al., 2010, p.3776). More recently, a review conducted by Waisman Campos et al., (2016) highlighted the detrimental effects of nicotine on various neuropsychological domains. Memory, attention, and executive functioning were found to decline in middle aged adults classified as heavy smokers.

Although the aforementioned reviews provide evidence about neuropsychological impairments as a result of chronic tobacco smoking, their findings should be considered cautiously. In fact, many of the studies included in these reviews didn’t

account statistically for confounding factors such as psychiatric disorders and comorbid alcohol and/or other substance abuse, as highlighted by the same authors.

Currently, there is no clear link between chronic tobacco smoking and neuropsychological impairments and no evidence derived from meta-analyses. It is therefore essential to investigate quantitatively the association between chronic tobacco smoking and possible neuropsychological impairments.

2. Literature search

The “Preferred Reporting Items for Systematic Review and Meta Analysis” (PRISMA) guidelines (Liberati et al., 2009) and the “Meta Analysis for Observational Studies in Epidemiology” (MOOSE) guidelines (Stroup et al., 2000) were utilized to identify and assess relevant papers to include in this review.

The inclusion criteria aimed to utilize any trial methodology, include chronic tobacco smokers aged 18 years or over, be published in English language literature and be categorized as case control, longitudinal, and/or cross-sectional studies. Longitudinal cohort studies were also included, however only the baseline data was used for this review so they were classified as cross-sectional studies. Additionally, the studies had to provide the name or a description of the neuropsychological tests utilised to assess the cognitive functions of individuals. This would have allowed them to be sorted in different neuropsychological domains (Baldacchino et al., 2012).

The exclusion criteria used were the follows:

(A) Cohorts including individuals under 18 years of age.

(B) Cohorts including individuals with current illicit polydrug use and dependence.

(C) Cohorts including individuals diagnosed with any Axis-1 Psychiatric Illness (as defined by DSM IV/V).

(D) Cohorts including individuals with alcohol dependence.

(E) Cohorts including individuals with any history of serious head injury.

(F) Cohorts including individuals who were HIV serotype positive.

(G) Studies with no healthy non-smokers controls as comparator groups

A computer based literature search was conducted in January 2017 to identify relevant papers for the current systematic review and meta-analysis. The following databases were used: Pubmed (1964 to 11th January 2017), Psychinfo (1980 to 17th January 2017), Ovid Medline (1946 to 18th January 2017), Embase (1974 to 18th January 2017), and Cochrane Central (1966 to 17th January 2017). The search term used were *chronic* OR *long term* AND *nicotine* OR *tobacco* OR *smoking* AND *cognitive tests* OR *deficits* OR *impairments* OR *neuropsychological tests* OR *deficits* OR *impairments*. Subsequently, the *cognitive tests* and *neuropsychological tests* search terms were removed and the names of specific cognitive tests were inserted, thus the databases searched again. Names of cognitive tests included '*Wechsler Adult Intelligent Scale', 'Two Back Test', 'Stroop Test', 'California Verbal Learning Test', 'Trail Making Test', 'Ray Auditory Verbal Learning Test', 'Verbal Fluency', 'Wisconsin Card Sorting Test',* and *'Gambling Test'.*Tobacco companies such as imperial brands tobacco and Philip Morris international were contacted to inquire about any relevant research regarding the cognitive effects of cigarette smoking. Although, the authors of the current study wish to state that tobacco companies were not provided with access to the drafts or to the final version of the manuscript prior to journal submission. Lastly, the references of the selected papers were inspected and a snowballing technique was used to identify further relevant studies.

3. Analysis

Meta-analytic techniques were employed to reach a quantitative estimate for the impact of chronic tobacco smoking on eight neuropsychological domains, including: Cognitive Impulsivity, Motor Impulsivity, Non-Planning impulsivity, Cognitive Flexibility, Attention, Intelligence, Short Term Memory, and Long-Term Memory. These domains were identified from the neuropsychological tests utilised by the studies included in the review following the guidelines of Baldacchino et al. (2012) (see Supplementary Table 1). As the studies employed different neuropsychological tests to measure the impact of chronic tobacco smoking on the above domains, Standardized Mean Difference (SDM) effect sizes were used. A random effect model was preferred over a fixed effect model as the studies included in the review were not functionally equivalent and the assumption that the true effect size was the same in all studies was not met (Borenstein et al., 2007). Heterogeneity between the studies included in the meta-analysis was assessed by Cochran's Q and I^2 tests (Higgins et al., 2003; Cochran, 1950).

The effect sizes for the individual studies and the respective summary effect sizes for each neuropsychological domain were computed through the Comprehensive Meta-Analysis Version III software (CMA, 2017). A large effect size would have been determined by a value of 0.8, a medium effect size would have been determined by a value of 0.5, and a small effect size would have been determined by a value of 0.2 (Cohen, 1988). The criterion for statistical significance was considered to be $p<0.05$ (Cohen, 1994).

A meta-regression was conducted to identify significant relationships between each of the continuous moderator variables (chronicity of nicotine smoking, age and educational status) and the effect size. The meta-regression was only performed in the neuropsychological domains in which eight or more studies were available (Thompson & Higgins, 2002).

3.1 Publication Bias

In scientific literature there is the tendency to publish more frequently studies with statistically significant results than studies deemed to be statistically insignificant and with low effect sizes (Dickersin, 2005; Hedges, 1989). Thus, there is a possibility that studies included in a meta-analysis would be biased and consequently reflected in the results of the quantitative synthesis. In order to assess the possible presence of such bias a visual inspection of funnel plots was carried out alongside the statistical computation of Fail Safe N (Orwin, 1983). Fail Safe N refers to the number of missing studies that would allow to determine how many of these studies would bring the overall effect of the current meta-analysis to a specified level other than zero and that would be needed to change the result from significant to non-significant (Orwin, 1983; Rosenthal, 1979).

3.2 Assessment of study quality

The National Institute of Health (NIH) cross-sectional and case-control quality assessment tools were utilized to evaluate the quality of the papers included in the review. Studies were classed as ‘poor’, ‘fair’, or ‘good’ (“Study Quality Assessment Tools.,2017”). The quality of the papers was assessed by three reviewers (AB, ST,

and AAC) in order to reduce bias. Of the 24 studies included in the meta-analysis, 11 studies were classified as ‘Fair’, 9 studies were classified as ‘Good’, and 4 studies as ‘Poor’. These studies were categorized as ‘poor’ (Deary et al., 2003; Hatta et al., 2006; Hill, 1989; Launer et al., 1996) because they didn’t account statistically for several confounding factors such as age, gender, and years of education.

The four studies that were classified as ‘poor’ were included in the quantitative synthesis to avoid reducing the sample size and consequently decreasing the statistical power of the meta-analysis (Hedges, & Pigott, 2001) as no relevant data were missing and they didn’t present serious methodological flaws. A sensitivity analysis conducted *a posteriori* revealed the absence of bias to the results which justified their inclusion.

4. Results

In total, 2611 papers were identified through the search conducted on relevant databases in combination with other sources. Papers were screened for relevance and 1837 studies excluded. Subsequently, studies were assessed for eligibility through title and abstract inspection and duplicates were removed, eliminating 717 papers. The remaining 62 papers were screened for eligibility utilizing the inclusion and exclusion criteria. Finally, 15 case-control studies and 9 cross-sectional studies were included in the quantitative synthesis (Fig.1; QUOROM).

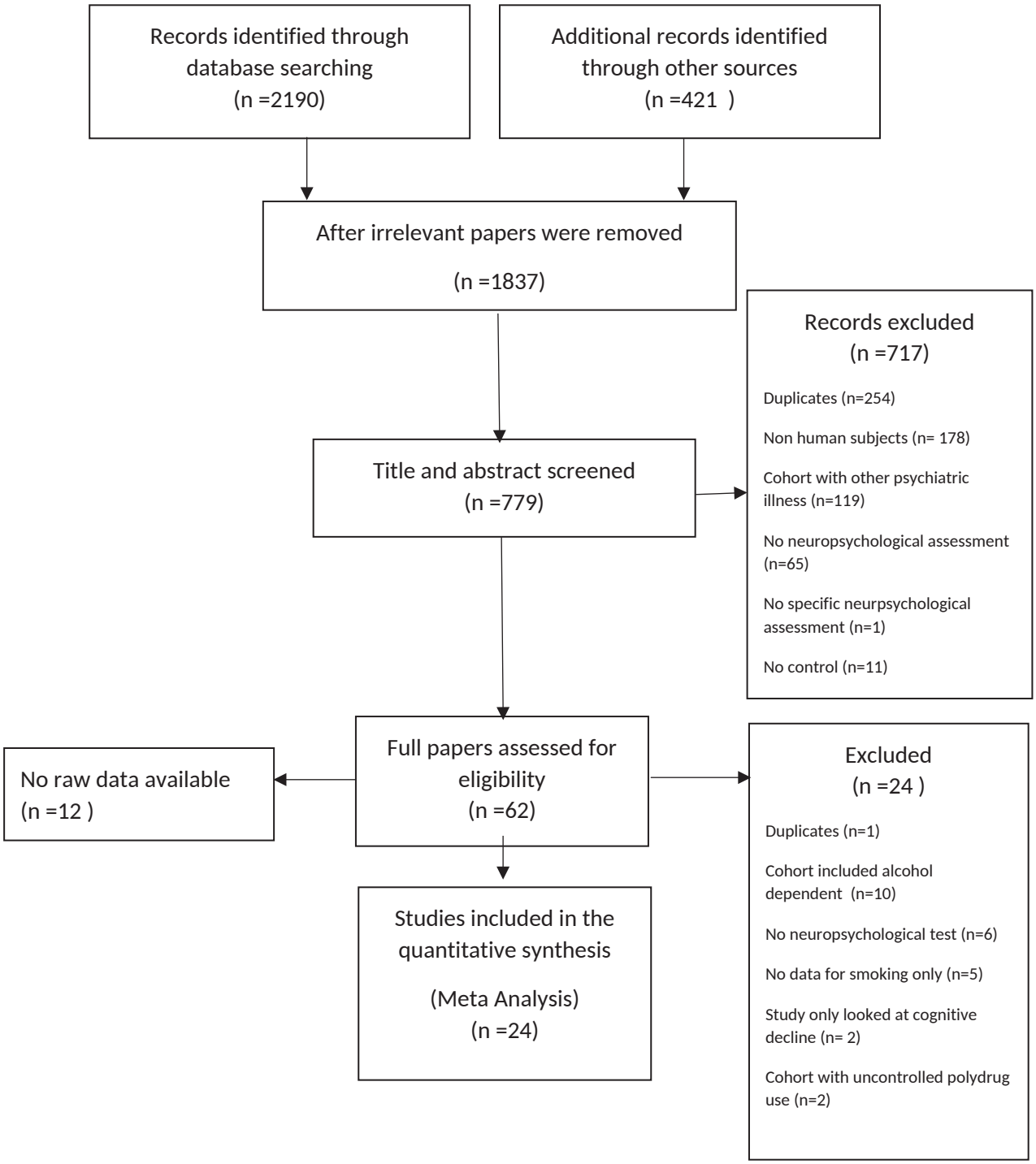

Figure 1. Neuropsychological associations with Chronic Nicotine Use: Quality of Reporting Of Meta-analysis (QUOROM): 1946-2017

Several studies included in the quantitative synthesis reported data from different comparator groups (e.g. ‘quitters’, ’light smokers’, and ‘occasional smokers’). Thus, in accordance with the aim of the study and with the inclusion and exclusion criteria only the appropriate comparator groups were included in the meta-analysis. These are presented in Table 1 below alongside the excluded comparator groups.

Table 1. Comparator groups included and excluded in the meta-analysis

	N
Included comparator groups	
Chronic/heavy smokers	24
Never/Non-smokers	24
Excluded comparator groups	
Light smokers	1
Medium/moderate smokers	2
Ex-smokers (recent and long-term)	10
Occasional/non-dependent smokers	3
Never smoked-current alcohol drinkers	1
Ex-smokers-ex alcohol drinkers	1
Ex-smokers-current alcohol drinkers	1
Current smokers-ex alcohol drinkers	1
Current smokers-current alcohol drinkers	1
Dependent to Marijuana	1
Long-term abstinent alcohol dependents - smokers	1
Long-term abstinent alcohol dependents-non smokers	1

Note. Out of the 24 studies included in the meta-analysis only six studies compared chronic nicotine smokers with non-smokers without using other comparator groups. The majority of the studies used more than one comparator but these groups were excluded from the meta-analysis.

Demographic data were extracted from a total of 3756 chronic nicotine smokers and 7669 non-smokers healthy controls. The mean age range of individuals varied from 21.5 years (Chamberlain et al., 2012) to 76.8 years old (Galanis et al., 1997). Several studies compared individuals within particular age groups, such as young adults (Chamberlain et al., 2012; Deary et al., 2003; Paelecke-Habermann et al., 2013; Smolka et al. 2004; Yakir et al., 2006) middle aged adults (Carim-Todd et al., 2015; Durazzo et al., 2012; Friend et al., 2005; Hatta et al., 2006; Kalmijn et al., 2002;Luhar et al., 2013; Sabia et al., 2012, Schinka et al., 2002), and elderly (Chen et al., 2003; Galanis et al., 1997; Hill et al., 1989; Launer et al., 1996; Razani et al., 2004). Average years of education varied from 2.9 years (Chen et al., 2003) to 16 years (Carim-Todd et al., 2015). Information about smoking pack years was extracted from just 8 studies. The lowest average pack years were 4.26 (Luhar et al.,2013), while the highest were 73.73 (Razani et al.,2004). The studies were conducted in 11 different countries, particularly: USA, Israel, Egypt, Netherlands, UK, Taiwan, Japan, Sweden, China, Germany, and Australia. The demographic data and the quality assessment for each study are presented in Table 2 below.

Table 2. Demographic data

Paper	Quality	Country	Type of study	Chronic Nicotine smokers group					Non-smokers control group				
				n	Age Mean (SD)in years	Gender	Years of education Mean (SD) or %	Pack years	n	Age Mean (SD) in years	Gender	Years of education Mean (SD) or %	Pack years
Carim-Todd et al. (2016)	Fair	USA	Case-control	23	34.75 (1.667)	9M 14F	18.2%>16 years	n.a.	25	33.68 (1.61)	11M 4F	40%>16 years	n.a.
Chamberlain et al. (2012)	Fair	UK and USA	Case-control	37	21.5 (3.58)	28M 9F	86.8% College or above	n.a.	177	21.11 (3.13)	128M 49F	91.6% College or above	n.a.
Chen et al. (2003)	Good	Taiwan	Cross-sectional	195	72.5 (6.3)	195M	2.9 (3.4)	n.a.	68	72.3 (6.2)	68M	4.4 (3.8)	n.a.
Deary et al. (2003)	Poor	UK	Cross-sectional	34	80	n.a.	n.a.	n.a.	205	80	n.a.	n.a.	n.a.
Durazzo et al. (2012)	Good	USA	Case-control	27	48.9 (8.4)	23M 4F	14.4 (1.6)	29.8 (14.0)	30	44.4 (8.7)	26M 4F	15.7 (2.0)	0
Elwan et al. (1996)	Fair	Egypt	Case-control	60	n.a.	60M	n.a.	n.a.	114	n.a.	69M 45F	n.a.	n.a.
Ernst et al. (2001)	Fair	USA	Case-control	14	n.a.	6M 8F	n.a.	18.54	9	n.a.	3M 6F	n.a.	0
Friend et al. (2005)	Fair	USA	Case-control	84	n.a.	n.a.	n.a.	n.a.	74	n.a.	n.a.	n.a.	n.a.
Galanis et al.(1997)	Good	USA	Cross-sectional	921	76.8 (4.2)	921M	12% College or above	n.a.	1174	78.4 (4.8)	1174M	21% College or above	n.a.
Hatta et al. (2006)	Poor	Japan	Cross-sectional	130	62.27 (9.75)	n.a.	7.66 (2.41)	n.a.	295	63.1 (9.2)	n.a.	10.4 (2.3)	n.a.
Hill et al. (1989)	Poor	USA	Case-control	11	73.7 (5.5)	3M 8F	13.0 (3.0)	n.a.	53	71.0 (4.6)	14M 39F	13.4 (3.4)	n.a.
Hill et al. (2003)	Good	Sweden	Case-control	164	n.a.	n.a.	n.a.	n.a.	438	n.a.	n.a.	n.a.	n.a.
Kalmijn et al. (2002)	Good	Netherlands	Cross-sectional	530	n.a.	268M 261F	n.a.	22.3 (13.5)	618	n.a.	205M 413F	n.a.	0

Launer et al.(1996)	Poor	Netherlands	Cross-sectional	110	74.1 (4.0)	110M	88.6%>6 years	42.87	91	75.7 (5.1)	91M	84.6>6 years	0
Luhar et al. (2013)	Fair	USA	Case-control	6	47.0 (7.8)	4M 2F	14.3 (3.3)	4.26 (3.25)	7	50.4 (9.8)	4M 3F	14.3 (2.1)	0
Lyvers et al. (2013)	Fair	China and Australia	Case-control	215	n.a.	n.a.	n.a.	n.a.	104	n.a.	n.a.	n.a.	n.a.
Lyvers et al. (2014)	Fair	Australia	Case-control	61	n.a.	n.a.	n.a.	n.a.	86	n.a.	n.a.	n.a.	n.a.
Paelecke-Habermann et al. (2013)	Good	Germany	Case-control	27	25.85 (7.99)	7M 20F	n.a.	7.54	25	24.84 (7.47)	7M 18F	n.a.	0
Paul et al. (2006)	Good	Australia	Case-control	62	36.42 (13.25)	28M 34F	13.94 (2.09)	n.a.	62	35.52 (15.51)	32M 30F	14,58 (2.35)	n.a.
Razani et al. (2004)	Fair	USA	Case-control	13	63.62 (9.23)	4M 9F	13.28 (2.29)	73.73 (26.48)	66	69.06 (7.88)	9M 57F	14.96 (2.05)	2.00 (2.53)
Sabia et al. (2012)	Fair	UK	Cross-sectional	730	55.22	468M 262F	n.a.	n.a.	3575	55.66	2398M 1177F	n.a.	n.a.
Schinka et al. (2001)	Good	USA	Cross-sectional	174	38.41 (2.49)	174M	12.88 (2.26)	20.29 (11.97)	204	38.36 2.25	204M	12.76 (2.25)	0
Smolka et al. (2004)	Fair	Germany	Case-control	37	24.9 (3.2)	37M	n.a.	9.04	18	27.1 (4.3)	18M	n.a.	0
Yakir et al. (2006)	Good	Israel	Case-control	91	24.2 (2.1)	91F	13.4 (1.4)	n.a.	151	23.1 (2.1)	151F	13.7 (1.7)	n.a.

Note. Several studies presented demographic data without providing the Mean and Standard Deviation (SD). These data are described in the above table as they were reported in the respective studies. N= total number in study; M= Males; F= Females; n.a.= not applicable; Pack Years= a person's cigarette consumption calculated as the packs of cigarettes smoked per day, multiplied by the length of consumption in years.

4.1 Neuropsychological domains

Quantitative data extracted from the selected studies revealed the possibility to conduct 62 effect size measurements. These are illustrated in Figures 2-9 below. Fail Safe N results revealed the absence of publication bias for the inclusion of studies testing *cognitive impulsivity, non-planning impulsivity, cognitive flexibility, attention, intelligence, short and long-term memory,* as a reasonable number of studies would be required to change the effect sizes from significant to non-significant, with the exception for motor impulsivity ($p<0.05$). Fail Safe N tests results are related effect sizes are listed in Table 3 below.

Table 3. Fail Safe N Tests Results

Cognitive Domains	*N*	*p*	Fail safe N
Cognitive impulsivity	6	0.003**	101
Motor impulsivity	4	0.248	0.00
Non planning impulsivity	8	0.000**	127
Cognitive flexibility	9	0.022*	161
Attention	11	0.003**	26
Intelligence	6	0.015*	34
Short term memory	11	0.001**	100
Long term memory	6	0.002**	51

Note. P= Significance,* significant at the $p<0.05$ level, ** significant at the $p<0.01$ level.
N= Total number of studies

For *Cognitive Impulsivity* a significant and large effect size of 0.881 was found in favour of the non-smokers control group ($z=2.998$, $p<0.005$) revealing the tendency for chronic tobacco smokers to opt for small immediate rewards over larger delayed rewards in contrast to non-smokers. Results of *Q* and I^2 tests Indicated

heterogeneity between the six pooled studies (Q=114.12,*p*=0.00, I^2=95.62). Details are depicted in Figure 2 below.

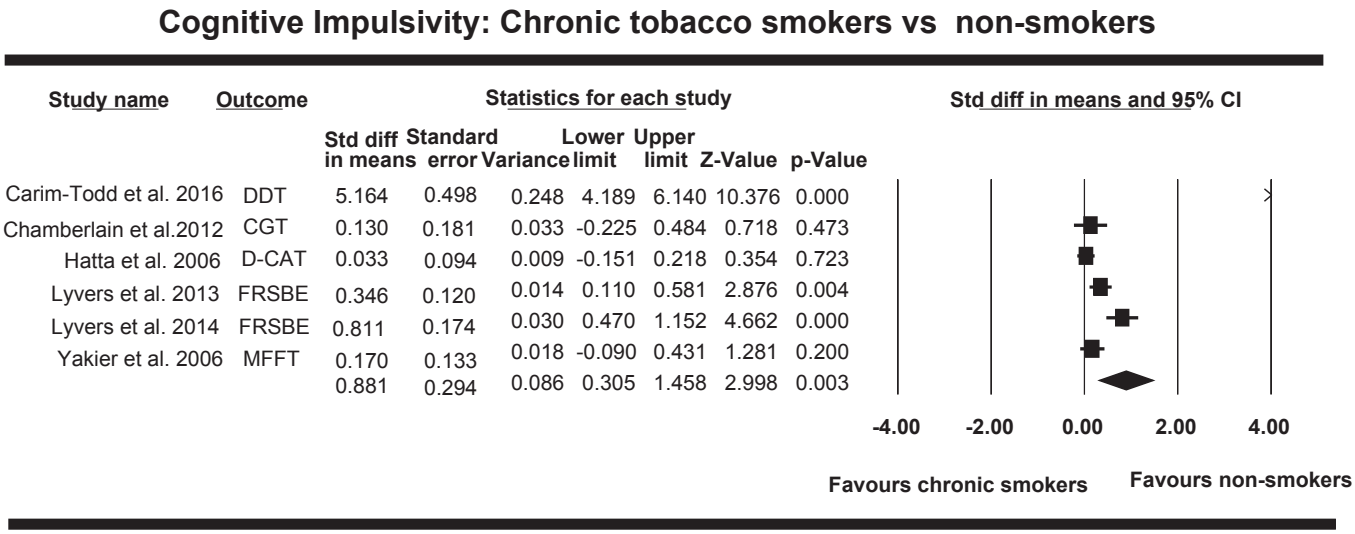

Figure 2. Cognitive Impulsivity Forest Plot. (std diff= standard difference; Z value= one sample Z statistic; p value=probability that Z statistics is significantly different than 0; lower limit= lower limit of the 95% confidence interval for the effect size; upper limit= upper limit of the 95% confidence interval for the effect size; DDT= Delay Discounting Test; CGT= Cambridge Gambling Task; D-CAT= Digit Cancellation Test; FRSBE=Frontal Systems Behavior Scale; MFFT=Matching Familiar Figures Test)

For *Motor Impulsivity* a non-significant effect size of 0.105 was found in favour of the non-smokers control group (z=1.156, p=0.248). Results of *Q* and I^2 tests Indicated homogeneity between the four pooled studies (Q=1.151,*p*=0.68, I^2=0.00) . Details are illustrated in Figure 3 below.

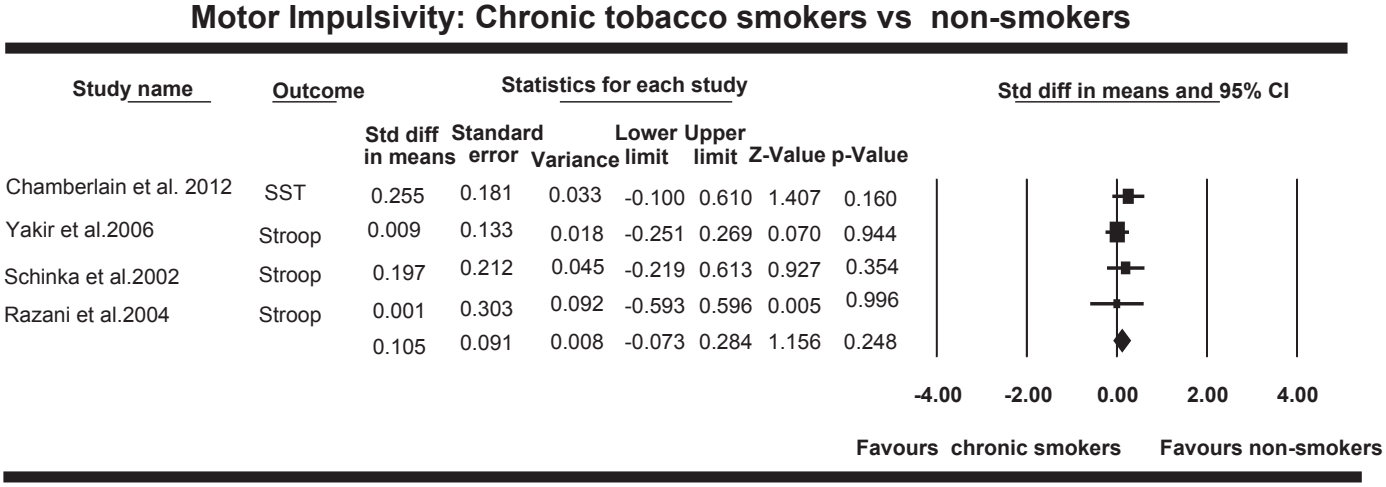

Figure 3. Motor Impulsivity Forest Plot.(std diff:=standard difference; Z **value**:=one sample Z statistic; p value= probability that Z statistics is significantly different than 0; lower limit= lower limit of the 95% confidence interval for the effect size; upper limit= upper limit of the 95% confidence interval for the effect size; SST= Stop Signal Task; Stroop= Stroop Task)

For *Non Planning Impulsivity* a significant and medium effect size of 0.505 was found in favour of the non-smokers control group (z=3.615,*p*<0.001), showing a lesser capacity for chronic tobacco smokers to solve problems by thinking ahead and by searching for an appropriate solution in contrast to non-smokers. Results of *Q* and I^2 tests Indicated heterogeneity between the eight pooled studies (Q=49.564,*p*=0.00, I^2=85.88). Details are depicted in Figure 4 below.

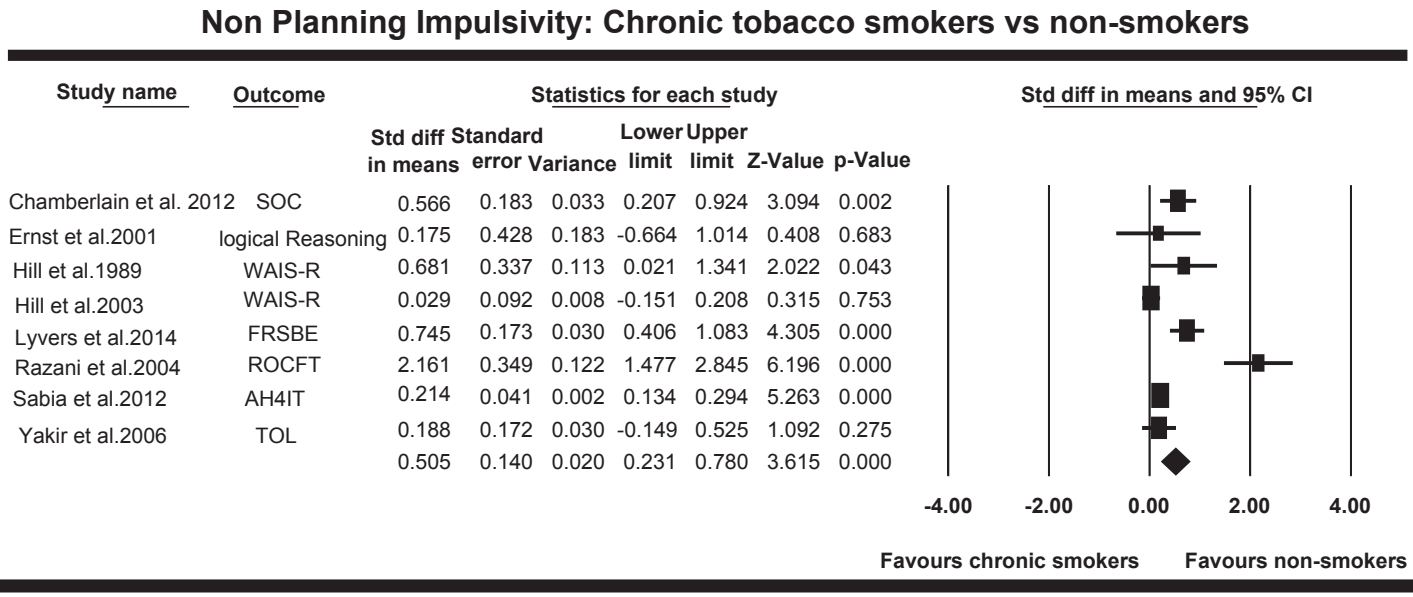

Figure 4. Non Planning Impulsivity Forest Plot. (std diff= standard difference; Z value= one sample Z statistic; p value: probability that Z statistics is significantly different than 0; lower limit= lower limit of the 95% confidence interval for the effect size; upper limit= upper limit of the 95% confidence interval for the effect size; SOC= Stockings of Cambridge Test; Logical Reasoning=Logical Reasoning Tests; WAIS-R=Wechsler Adult Intelligence Scale Test; FRSBE=Frontal Systems Behavior Scale; ROCFT= Rey–Osterreith Complex Figure Test;AH4IT= Alice Heim 4 Test, TOL=Tower of London Test)

For *Cognitive Flexibility* a significant effect size of 0.450 was found in favour of the non-smokers control group (z=2.265, $p<0.05$), indicating an impaired capacity for chronic tobacco smokers to generate appropriate behavioral responses while switching between cognitive processes in contrast to non-smokers. Results of *Q* and I^2 tests Indicated heterogeneity between the nine pooled studies (Q=112.10, $p=0.00$, $I^2=92.86$). Details are depicted in Figure 5 below.

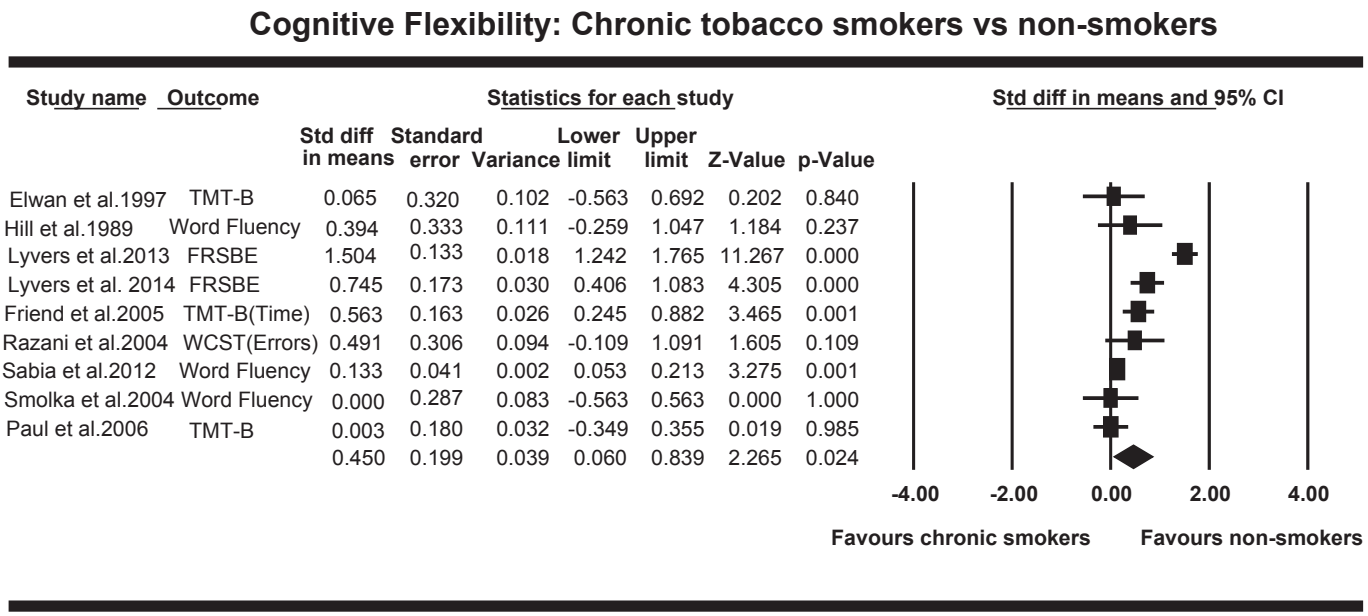

Figure 5. Cognitive Flexibility Forest Plot. (std diff= standard difference; Z value= one sample Z statistic; p value: probability that Z statistics is significantly different than 0; lower limit= lower limit of the 95% confidence interval for the effect size; upper limit= upper limit of the 95% confidence interval for the effect size; TMT-B: Trail Making Test; Word Fluency=Word Fluency Task; FRSBE=Frontal Systems Behavior Scale; WCST=Wisconsin Card Sorting Test)

For *Attention* a significant and small effect size of 0.196 was detected in favour of the non-smokers control group (z=2.944, p<0.005), showing a slightly better capacity for non-smokers to attend relevant inputs while rejecting irrelevant information and to detect unpredictable signals during prolonged periods of concentration in contrast to chronic tobacco smokers. Results of Q and I^2 tests Indicated heterogeneity between the 11 pooled studies (Q=14.66,p=0.15,I^2=31.76). Details are depicted in Figure 6 below.

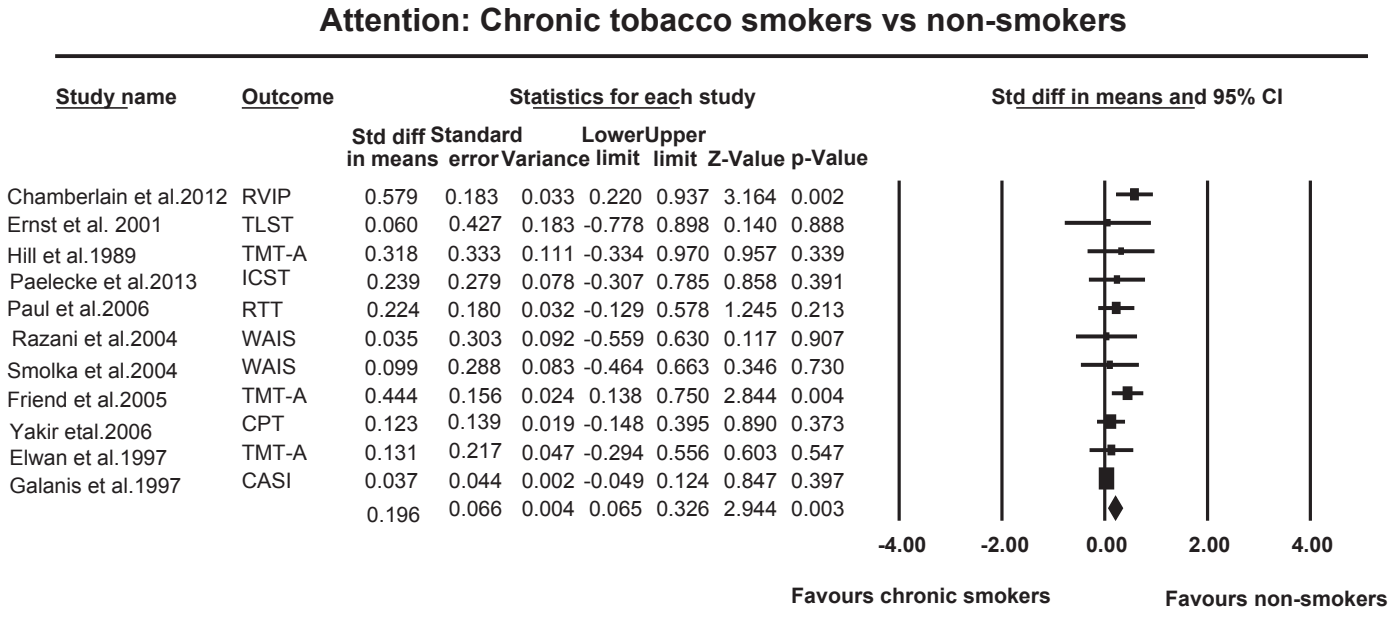

Figure 6. Attention Forest Plot. (std diff= standard difference; Z value= one sample Z statistic; p value: probability that Z statistics is significantly different than 0; lower limit= lower limit of the 95% confidence interval for the effect size; upper limit= upper limit of the 95% confidence interval for the effect size; RVIP=Rapid Visual Information Processing Task; TLST= Two Letter Search Task; TMT-A=Trail Making Test; ICST=Ice Cream Seller Task; RTT=Reaction Time Test; WAIS=Wechsler Adult Intelligence Scale; CPT=Cognitive Performance Test; CASI=Cognitive Abilities Screening Test)

For *Intelligence* a significant and small effect size of 0.164 was found in favour of the control group (z=2.423, p<0.05), indicating the tendency for chronic tobacco smokers to perform worse than non-smokers in several domains related to the overall intelligence and cognitive capacity of individuals such as verbal reasoning, verbal comprehension, and perceptual organization. Results of *Q* and I^2 tests indicated heterogeneity between the six pooled studies (Q=26.23,p=0.00, I^2=80.93). Details are depicted in Figure 7 below.

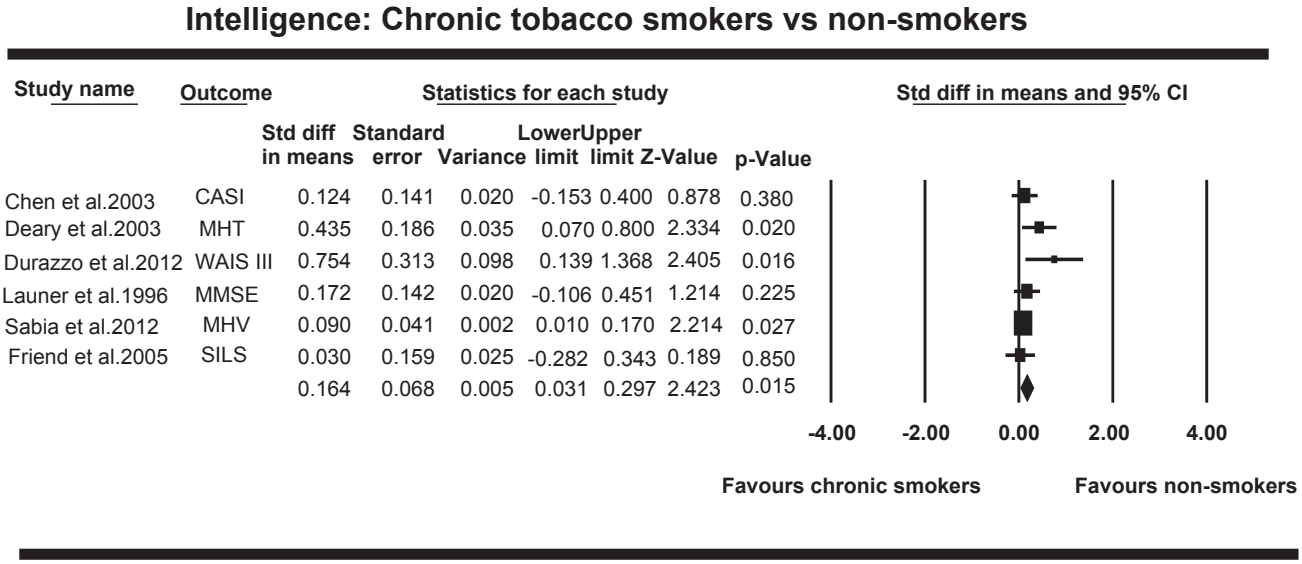

Figure 7. Intelligence Forest Plot. (std diff:=standard difference; Z value:=one sample Z statistic; p value: probability that Z statistics is significantly different than 0; lower limit= lower limit of the 95% confidence interval for the effect size; upper limit= upper limit of the 95% confidence interval for the effect size; CASI=Cognitive Abilities Screening Test; Moray House Test; WAIS=Wechsler Adult Intelligence Scale; MMSE= Mini Mental State Examination; MHV= Mill Hill Vocabulary Test; SILS= Shipley Institute of Living Scale)

For *Short Term Memory* a significant effect size of 0.413 was found in favour of the non-smokers control group (z=3.537, p<0.001), showing a better capacity for non-smokers to recall information presented shortly before in comparison to chronic

tobacco smokers. Results of *Q* and I^2 tests indicated heterogeneity between the 11 pooled studies (Q=33.44,*p*=0.00 I^2=70.10) . Details are depicted in Figure 8 below.

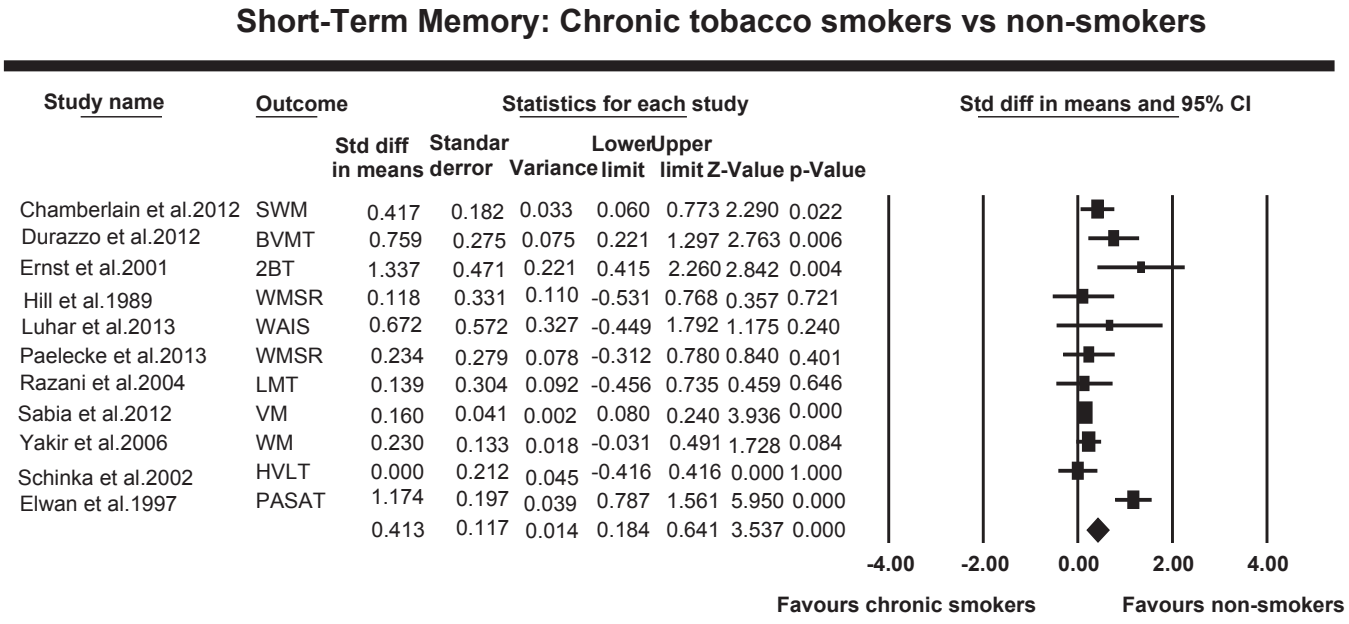

Figure 8. Short Term Memory Forest Plot. (std diff= standard difference; Z value:=one sample Z statistic; p value:=probability that Z statistics is significantly different than 0; lower limit= lower limit of the 95% confidence interval for the effect size; upper limit= upper limit of the 95% confidence interval for the effect size; SWM= Spatial Working Memory Task; BVMT= Brief Visuospatial Memory Test; 2BT= Two Back Test; WMSR= Wechsler Memory Scale; WAIS= Wechsler Adult Intelligence Scale; LMT= Letter Memory Test; VM= Verbal Memory Test; WM= Working Memory Test; HVLT= Hopkins Verbal Learning Test; PASAT= Paced Auditory Serial Addition Test)

For *Long Term Memory* a significant effect size of 0.621 was detected in favour of the non-smokers control group (z=3.539, *p*<0.001), indicating a better capacity for non-smokers to retain information over longer periods of time in contrast to chronic tobacco smokers. Results of *Q* and I^2 tests indicated heterogeneity between the six pooled studies (Q=16.49,*p*=0.006 I^2=69.68). Details are depicted in Figure 9 below.

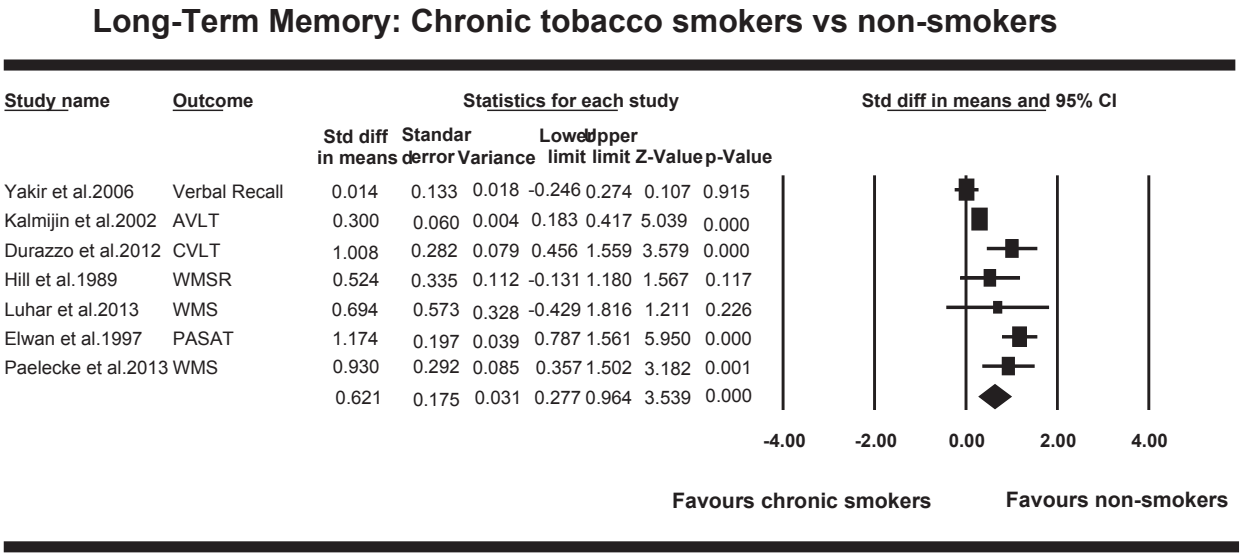

Figure 9. Long Term Memory Forest Plot. (std diff= standard difference; Z value= one sample Z statistic; p value= probability that Z statistics is significantly different than 0; lower limit= lower limit of the 95% confidence interval for the effect size; upper limit= upper limit of the 95% confidence interval for the effect size; Verbal Recall= Verbal Recall Test; AVLT= Auditory Verbal Learning Test; CVLT= California Verbal Learning Test; WMSR= Wechsler Memory Scale Revised; WMS= Wechsler Memory Scale; PASAT= Paced Auditory Serial Addition Test)

4.2 Subgroup analysis: Meta-regression

There were not enough studies to have the power to test an association between chronicity of tobacco smoking and educational status as the moderator variables and all the neuropsychological domains. We were limited in reporting the Z value and associated *p* values in Attention and Short-Term Memory for age. It identified a significant effect in Attention (slope Z= -2.27, *p*=0.02) and a non-significant effect in Short Term Memory (slope Z= -1.31, *p*=0.19) (Figures 10a and 10b) with older chronic tobacco smokers exhibiting greater neuropsychological impairment when compared with younger peers.

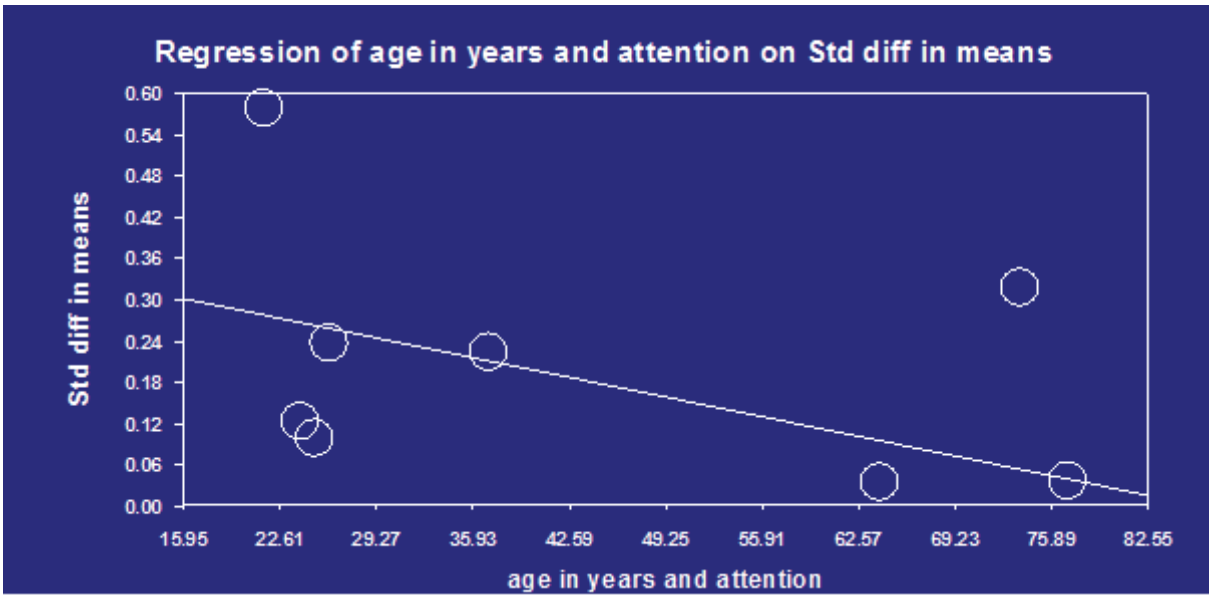

Figure 10 a. Meta-regression of chronic nicotine users by age with respect to Attention

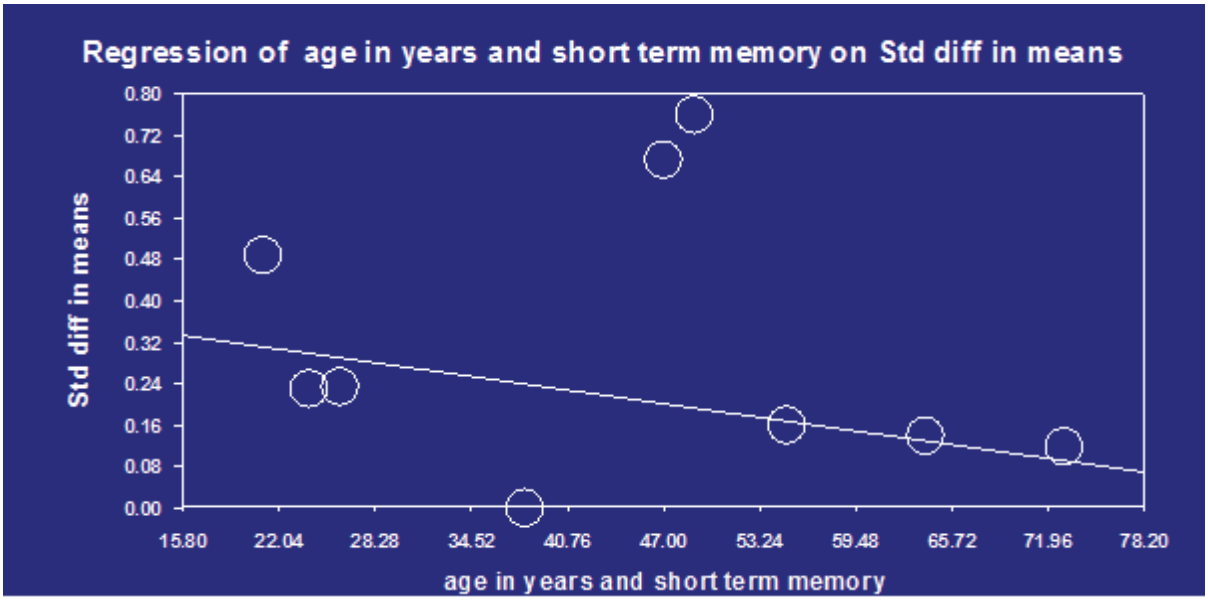

Figure 10 b. Meta-regression of chronic nicotine users by age with respect to Short Term Memory

5.Discussion

5.1 Key findings

We conducted a meta-analysis with the aim to provide a quantitative synthesis for the associations between chronic tobacco smoking and neuropsychological functions of individuals across a wide age range. The results underlined a cross-sectional association between chronic tobacco smoking and cognitive impairments in seven neuropsychological domains such as cognitive impulsivity, non-planning impulsivity, cognitive flexibility, attention, intelligence, short term memory, and long-term memory. This supports the findings of Durazzo et al., (2010). The above results illustrated that the most robust impairments are related to the cognitive impulsivity domain while the least robust impairments are related to the attention and intelligence domains. Fail Safe N results are sufficiently high to exclude possible publication bias (see Table 6).

These results are in line with the review conducted by Waisman Campos et al. (2016) that illustrated a decline in cognitive areas such as attention, memory and Executive functioning in middle aged adults considered to be heavy tobacco smokers, and with reviews that indicated a significant cognitive decline in elderly exposed chronically to tobacco (Almeida et al.,2002; Anstey et al., 2007; Ott et al., 2004; Peters et.al, 2008), suggesting that chronic smokers may be at major risk for dementia compared to non-smokers. The largest effect size (SMD=0.881) was found in favor for the cognitive impulsivity domain. This result support previous research (Bloom et al., 2013; Mitchell, 2004; Sweitzer et al., 2008) that illustrated how chronic nicotine consumption is strongly related to an increase in impulsivity and to a devaluation of future larger rewards over most immediate and smaller

rewards in temporal discounting tasks. No cross-sectional association was found between motor impulsivity and chronic smoking, contrasting the findings of a recent review conducted by Kale et al. (2018) to assess the magnitude of the relationship between different dimensions of impulsivity and tobacco smoking. A possible explanation for the current findings could be related to the small number of studies included in the meta-analysis assessing the link between motor impulsivity and chronic smoking (n=4). Thus, indicating the possible presence of bias towards a non-statistically significant association (Higgins & Thompson, 2002).

5.2. Strengths and Limitations

A search technique comprising online databases and scientific journals was employed to identify studies to include in the quantitative synthesis. Generic terms were subsequently substituted with names of neuropsychological tests. The inclusion and exclusion criteria were rigorous, thus aiding the exclusion of confounding factors such as psychiatric illness and polydrug use. Other possibly confounding factors that could have impacted the results of the studies included in the review encompassed demographic variables such as gender, age, educational level, socioeconomic status, and co-occurring consumption of alcohol and other drugs. Previous research demonstrated that these variables could affect negatively the cognitive ability of individuals (Mani et al., 2013; Murman, 2015; Piumatti, 2018;Salthouse 2009). Confounding factors were accounted for in the majority of the studies included in the meta-analysis, although several studies controlled statistically for just one or few variables and/or differed in relation to which confounders were reported (Chen et al., 2002; Friend et al., 2005; Galanis et al.,

1997; Hatta et al., 2006; Launer et al., 1996; Paelecke-Habermann et al., 2013; Paul et al., 2006; Schinka et al., 2001). Because of this, it wasn't possible to include confounding factors as moderators in the quantitative synthesis. This might be considered a limitation of our study.

The number of pack years varied consistently (from 4.26 to 73.73). This could be also considered a confounding factor as several studies included in the review revealed a negative link between the number of pack years and cognitive performance. Specifically, the cognitive performance of participants decreased as the number of pack years increased. Considering that just eight studies included in the current review reported the number of participants' pack years, it was not possible to assess whether unreported pack years from the other 15 studies would have influenced the outcomes of the current quantitative synthesis.

Methodological problems may also be related to the only inclusion of Non-Randomized Studies (NRS) such as case-control and cross-sectional studies in the review, as the non-random allocation of participants to groups could imply a large and unpredictable bias leading to over-estimations or under-estimations of treatment effects (Deeks et al., 2003). The inclusion of NRS in the review is due to the lack of Randomized Controlled Trials (RCTs) in the literature.

Another drawback of the current study may be related to the absence of longitudinal data in the meta-analysis as a consequence of avoiding bias related to earlier deaths of smokers compared to non-smokers. In fact, longitudinal data could be useful in determining developmental changes related to chronic smoking and neuropsychological impairments as age may influence significantly the cognitive

functions of individuals (Murman, 2015;Tucker-Drob, 2011). Furthermore, young people such as adolescents and young adults are particularly susceptible to the effects of addictive drugs such as nicotine due to their brain not being fully developed (Crews et al., 2007; Winters & Arria, 2011). Therefore, they might be at major risk of developing nicotine addiction during adulthood and might present specific developmental patterns related neuropsychological impairments associated to chronic smoking. These should be taken in consideration by future studies. The lack of information pertaining alternative methods for nicotine consumption could be considered as another limitation for this meta-analysis. In fact, it wasn't possible to identify studies fitting the inclusion and exclusion criteria that were testing the effect of alternative methods for nicotine administration on cognition, such as e-cigarettes and nicotine replacement therapies (NRT). Finally, the studies included in the current review differed consistently in relation to which subcategories of specific neuropsychological domains were tested. Older studies were also conducted utilizing outdated categories of specific domains. Therefore, in order to conduct the meta-analysis we deemed viable to encompass the results from each subcategory in eight main domains (see supplementary Table 1) that were sorted by assessing the neuropsychological tests utilized by the studies included in the review (Baldacchino et al., 2012). This might be considered an important limitation of our study.

5.3. Clinical relevance

There are more than one billion individuals exposed chronically to nicotine. While the impact of chronic tobacco smoking on the physical health of individuals is well

known, and several cessation programs and treatments have been developed to reduce morbidity and mortality rates related tobacco smoking, much is to be known about its' impact on the neuropsychology and cognitive functions of individuals. The current meta-analysis identified a cross-sectional association between chronic tobacco smoking and neuropsychological impairments. Neuropsychological impairments related to memory, attention, intelligence, and cognitive flexibility are reported to affect negatively the quality of life of individuals as they may undermine social relationships, prevent the performance of daily living activities, and may lead to neurological diseases such as Alzheimer (Kurz et al.,2003; Lindeboom, & Weinstein, 2004; Logsdon et al., 2002; Tarawneh, & Holtzman, 2012). Considering the negative impact of neuropsychological impairments on individuals' life, it suggested that pre-treatment neuropsychological assessments and tailored Cognitive Rehabilitation Treatments (CRTs) should be implemented in smoking cessation programmes. According to Rezapour et al. (2015) "CRT is a general term for specialized treatment procedures applied to improve cognitive functions such as attention, memory, problem solving, and planning" (p.292). Progress have been made in recent years in relation to the development of CRTs for individuals with cognitive impairments as a consequence of chronic exposure to opioids and alcohol, showing improvements in cognitive functions such as memory, processing speed, verbal skills, and problem solving (Ekhtiari, 2014; Rezapour et al., 2017). The current meta-analysis also illustrates that individuals exposed chronically to nicotine are significantly more impulsive in their decision-making behavior in contrast to non-smokers. Therefore, considering a cross-sectional association

between chronic smoking and impulsivity (Chase & Hoghart, 2011; Kale et al., 2018; Kolokotroni et al., 2011) specific treatments such as Cognitive Behavioural Therapy (CBT), Dialectical Behavioural Therapy (DBT), and Emotional Regulation strategies should be also implemented in smoking cessation programmes in order to prevent and reduce negative outcomes consequential to negative impulsive choices (Neto, & True, 2011).

Considering the current meta-analysis identified a cross-sectional association between chronic nicotine exposure and neuropsychological impairments, a direct causation cannot be inferred. It is well known that substances such as alcohol, opioids, and stimulants modulate and/or impair the cognitive abilities of individuals and increase impulsivity (e.g. Baldacchino et al., 2012; Mitchell et al., 2005; Reed et al., 2012; Verdejo-Garcìa et al., 2007). Taking into account the results of the current review, and that alcohol and drugs abusers are more likely to be chronic tobacco smokers (Lai et al., 2008; McCool & Richter, 2003; Richter et al., 2002), it is possible for the neuropsychological impairments identified in these populations to have also been confounded by the concomitant chronic nicotine administration. However, this notion is further complicated by a pre-morbid confounder such that individuals who are affected by neuropsychological impairments are more prone to become chronic smokers than individuals without cognitive impairments. To test this a longitudinal study would be required.

Furthermore, considering that nicotine may prime the use of other drugs such as opioids (and vice versa) through the interaction of opioid and nicotinic-cholinergic neurotransmitters systems (Britt & McGehee, 2008; Liu et al., 2013; Yoon et al.,

2015), and that nicotine administration involves the neurobiological reward pathways that also contribute to dependence in other substances (De Biasi & Dani, 2011; Jasinska et al., 2014; Rose, 2006), drug addiction treatment services should also support in smoking cessation programmes. This would not only help to avoid relapses, but it would also help to reduce neuropsychological impairments and cognitive decline.

6. Conclusion

The current meta-analysis identified a cross-sectional association between chronic tobacco smoking and impairments in seven neuropsychological domains. Future studies should focus on investigating the neuropsychological impact of nicotine administered chronically through alternative methods such as e-cigarettes and NRTs rather than in smoked tobacco. This would enable a further understanding of the drug's impact on the cognitive functions of individuals by ruling out possible confounding factors such as chemicals present in tobacco cigarettes. Furthermore, considering that in the literature there is a limited number of reviews exploring the link between chronic smoking and neuropsychological impairments of individuals across different age ranges, and that the age range of individuals included in the current study varied consistently (from 21.5 to 76.8 years), future meta-analyses should aim to investigate this association by focusing on specific age groups (e.g. adolescents).

In line with previous research and reviews conducted to assess the neuropsychological impact of different types of drugs such as opioids and alcohol, the results of the current quantitative synthesis underline the need to develop

specific CRTs to improve the cognitive functions of individuals exposed chronically to addictive substances. Finally, researchers and practitioners should also consider the complex effects of chronic nicotine consumption on cognition when treating individuals affected by drug addiction, and when conducting research to investigate the neuropsychological effects of other addictive substances. This would improve treatment outcomes.

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Conflicts of interests

AB has no conflict of interest with regard to the current work and has received educational grants from Schering Plough and has received research project funding from Merck Serono, Reckitt Benckiser and Indivior. JDS has no conflict of interest with regard to the current work and has received research funding via an honorarium associated with a lecture from Wyeth.ST has no conflict of interest with regard to the current work and has received funding from Merck Serono and Lundbeck. AAC has no conflict of interest.

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Supplementary Table 1. Neuropsychological Domains

Main domain	Subtypes	Other names	Definition	Tests
Cognitive Impulsivity		Delay discounting or urgency	Ability to opt for larger delayed rewards over smaller more immediate rewards.	
	(a)Reflection impulsivity		Decision making under ambiguity	IGT, MFFT, BIS, DDT
	(b)Risk taking		Decision making under risk	CGT, IGT, RDMT, GDT
Motor Impulsivity		Inhibitory control	Ability to suppress emotional, cognitive and behavioural responses	
	(a)Behavioural inhibition	Motor response inhibition	Process required to stop a planned movement	AGN,SS,Go/NoGo
	(b)Cognitive inhibition	Focused Attention	Process required to suppress a salient but conflicting stimulus while identifying less salient ones	ST
Non-Planning Impulsivity	Reasoning and problem solving	Central executive in working memory model Lack of pre-meditation	Ability to think ahead and actively search for an appropriate solution	TOL, SOC, ROCFT, PMT, TOH WAIS-III (Block Design, Matrix Reasoning), SSP, SWM
Cognitive flexibility		Rigidity	Ability to shift avenues of thought and action in order to perceive process and respond to situations in different ways.	
	(a) Reactive flexibility	Perseveration or shifting of perceptual set	Ability to realign a behavioural predispostition to altered contingencies	WCST, ST, IED, TMT, SCT, MCST
	(b) Spontaneous flexibility or fluency	Verbal and non verbal fluency	Requires the intrinsic generation of responses or alternatives	COWAT, FAS, VFT, RFFT, WAISIII (Similarities), RWT

Main domain	Subtypes	Other names	Definition	Tests
Attention	(a) Deployment	(a)Arousal		Observation
		(b)Focused and selected attention	Ability to reject irrelevant information while attending to relevant input.	WAIS-III (Digit Span), TMT, TEA, ST, AGN
		(c)Sustained attention	Readiness to detect rarely and unpredictable occurring signals over prolonged periods of time	PASAT,TOVA,TEA,CFT
	(b) Capacity/encoding or data processing		Ability for individuals to hold information in mind and process OR need to process tasks simultaneously	CVLT, RAVLT
		(a) Attention span		DSST, WAIS (Digit Symbol)
		(b) Reaction time or information processing speed		
Short term memory	Immediate memory	(a)Verbal memory	Reproduction, recognition or recall of information directly or some time after presentation.	LMT, RAVLT, CVLT, WAIS-III, VRM, WMSR, WRM, GNT, DFDBT, TBT
		(b)Visuo-spatial(non verbal) memory	Allow information to be evaluated and perhaps stored longer through rehearsal and coding	SWM, SSP. DMS, PRM, PAL, BVRT, PAL, SRM, WMSR, RCFT, PASAT, WAIS-III
Long term memory	(a)Explicit(declarative) memory	(a)Autobiographical, episodic or event memory	Records details salient to individuals life.Needs conscious thinking ‘Knowing That’	PRM, SRM, CVLT, RAVLT, PAL,ROCFT, WMSR, WAIS-III (Vocabulary)
		(b) Semantic memory	Meaning of words and concepts orpropositional knowledge (facts)	ROCFT, COWAT, GNT, WMSR,RBMT
	(b) Implicit (non declarative) or procedural memory	(a) Motor skill training	Does not need conscious thinking‘Knowing how’	
		(b) Priming or classical conditioning		

Main domain	Subtypes	Other names	Definition	Tests
Intelligence (IQ)	(a)Performance IQ		The capacity to think logically and to solve problems in novel situations, independent of acquired knowledge	WAIS-III, RPM, MMSE WASI, SHRS, NSCT, SILS, LPS
	(b) Verbal IQ		The ability to analyze information and solve problems using language-based reasoning	WAPIS, VAIS, WAIS-III,SFBT

AGN: Affective Go-NoGo (CANTAB), BIS: Barratt Impulsivity Scale, BLC: Big Little Circle, CGT: Cambridge Gambling Task (CANTAB), CFT: Continuous Performance Test, COWAT: Controlled Oral Word Association Test, CVLT:California Verbal Learning Test, DDT: Delay Discounting Test, DSST: Digit Symbol Substitution Test, FAS: Phonological Fluency Test, FFT: Finger TappingTest, GDT: Game and Dice Test, IED: Intra/Extra-Dimensional Set ShiftingTask (CANTAB), IST: Information Sampling Test, IGT: Iowa Gambling Task, MFFT: Matching Familiar Figures, MCST: Maudsley Card Sorting Test, PASAT: Paced Auditory Serial Addition Task, PMT: Proteus Maze Test, RAVLT:Rey Auditory Verbal Learning Test, RDMT: Rogers Decision Making Task, ROCFT: Rey–Osterreith Complex Figure Test, RT: Reaction Time, RWT: Regensburger Word Fluency Test, SCT: Logan Stop Change Task, SOC: Stockings ofCambridge (CANTAB), SSP: Spatial Span (CANTAB), SS: Stop Signal, SWM: Spatial Working Memory (CANTAB), ST: Stroop Test, TEA: Test of Everyday Attention, TMT: Trail Making Test, TOH: Tower of Hanoi, TOL: Tower of London(CANTAB), TOVA: Test of Variables of Attention, VFT: Benton Verbal Fluency Test, WCST: Wisconsin Card Sorting Test, and WAIS-III: Weschler Adult Intelligence Scale Third Edition, LPS:Lesitungs Prufsystems (German intelligence test battery),MMSE: Mini Mental State Evaluation, NSCT:Number Series Completion Test, RPM:Ravens Progressive Matrices, SHRS: Shipley-Hartford Retreat Scale,SILS:Shipley Institute of Living Scale, WAIS-III: Weschler Adult Intelligence Scale third edition, WASI: Wechler Abbreviated Scale of Intelligence, WAPIS: Weschler Adult Performance Intelligence Scale, VAIS: Verbal Adult Intelligence Scale, SFBT: Seguin Form Board Test.

Note. Adapted from ‘Neuropsychological consequences of chronic opioid use: A quantitative review and meta-analysis’ (Baldacchino et al. 2012)