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Structural Abnormalities in Gambling Disorder Using Voxel-Based Morphometry

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Master's thesis

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Gambling is a recreational activity popular across the globe, but maladaptive gambling behavior can pose serious, negative consequences to the gambler. Gambling disorder (GD) is a psychiatric disorder that focuses on these dysfunctional behaviors. In order to investigate the structural brain abnormalities in GD, a whole-brain exploratory analysis was carried out using voxel-based morphometry (VBM8). VBM8 was selected to enable direct comparison to an earlier study. There were no significant differences in global- or regional- gray and white matter volumes between GD patients and healthy controls (HC). These findings suggest that GD is not associated with macroscopic brain anatomical abnormalities or that anatomical abnormalities are too small compared to the individual variance to be detected with VBM8.

Key words: gambling disorder, addiction, behavioral addiction, MRI, voxel-based morphometry.

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Table of contents

List of Abbreviations

ACC	Anterior cingulate cortex
AUD	Alcohol use disorder
AUDIT	Alcohol use disorders identification test
CSF	Cerebrospinal fluid
CUD	Cocaine use disorder
dlPFC	Dorsolateral PFC
dmPFC	Dorsomedial prefrontal cortex
DOSS	Different onset, same slope
DSM-5	Diagnostic and Statistical Manual of Disorders, 5th edition
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
FWE	Family wise error
FWHM	Full width half maximum
GD	Gambling disorder
GLM	General linear model
HC	Healthy controls
ICD-11	International Classification of Diseases, 11th edition
IAD	Internet addiction disorder
IFG	Inferior frontal gyrus
IGD	Internet gaming disorder
LTP	Long term potentiation
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
NAcc	Nucleus Accumbens
OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
PG	Pathological gambling
ROI	Region of interest
SOGS	South Oaks Gambling Screening
SPM	Statistical parametric mapping
SUD	Substance use disorder

TIV	Total intracranial volume
UPPS-P	Urgency, premeditation, perseverance, sensation seeking, positive urgency, behavioral scale
VBM	Voxel-based morphometry
vmPFC	Ventromedial prefrontal cortex
VP	Ventral pallidum
VTA	Ventral tegmental area

1 Introduction

One pastime that is popular around the world entices individuals to spend their money without the guarantee of its return. The allure for this risky activity is the possibility of getting rich overnight or maybe winning a few extra dollars more than was spent. The other possibility, however, is to lose and never see the money again. Still, the possibility of winning has millions of people around the world buying lottery tickets, visiting casinos and placing bets. While many individuals gamble on occasion as a recreational activity, others may start spending more money and time on it than they should, succumbing to the darker side of the game.

Maladaptive gambling behavior can be broadly described as the impulsive urge to gamble regardless of negative consequences. These consequences include major financial problems, relationship problems like divorce, decrease in overall quality of life and increased risk for psychiatric comorbidities and suicide (Ioannidis et al., 2019). Excessive maladaptive gambling is referred to as gambling disorder (GD), previously known as pathological gambling (PG) (Quester & Romanczuk-Seiferth, 2015). With a global prevalence of 1.2 to 7.1%, GD is not an uncommon psychiatric problem due to the legal status of gambling and the ease at which individuals can access various forms of in-person and online gambling activities (Choi et al., 2017). Individuals that meet the criteria for GD have an insatiable urge and incessant preoccupation to gamble, becoming irritable when they try to quit (Potenza et al., 2019).

GD is labeled as a behavioral addiction and is classified under ‘Substance-Related and Addictive Disorders’ in the fifth edition of the *Diagnostic and Statistical Manual of Disorders* (DSM-5). Previously, GD was classified as an ‘Impulsive Control Disorder’ but evidence that it shares clinical features with traditional addiction disorders like substance use disorder (SUD) called for its reclassification (Grant et al., 2010; Petry et al., 2014; Weinstock et al.,

2013). The most recent revision of the International Classification of Diseases (ICD-11) soon followed suit and reclassified GD under the 'Substance Use and Related Disorders' group (Sztainert, 2018). Supporters of the reclassification argued that the behavioral, cognitive and neurobiological profile of GD is more similar to traditional addictions than impulse control disorders (Fauth-Bühler et al., 2017; Quester & Romanczuk-Seiferth, 2015). Furthermore, it is thought that GD can provide a clearer view into the pathophysiology of addiction due to the lack of neurotoxicity caused by drug use in patients with SUD (van Timmeren et al., 2018).

One neuroimaging method commonly used to investigate abnormalities in the brain is magnetic resonance imaging (MRI), which collects structural brain images that can be used to analyze brain shape, volume and thickness of either the whole-brain or specific regions of interest (ROI) (Morita et al., 2016). Voxel-based morphometry (VBM) is a popular tool used to carry out MRI analyses and aids in elucidating appropriate structural brain development and whether certain disorders and diseases show marked differences compared to healthy controls, which has clinical value for diagnosis and treatment. Unfortunately, the literature investigating GD brain structure is limited, contradictory and inconclusive on potential markers for the disorder.

Chapter 2 of this thesis will be a literature review to provide a background of GD and the VBM methodology, so the reader understands the underpinnings of the disorder and can appreciate the importance and goal of the project. Chapter 3 states the goals of the project, while chapters 4–5 provide the empirical component to test the hypotheses. Chapter 6 includes concluding thoughts and suggestions for future research.

2 Review of the Literature of Gambling Disorder

2.1 VBM Methodology

Due to advances in computational neuroanatomy over the last two decades, scientists are able to analyze neuroimaging data in a relatively straightforward manner. Voxel-based morphometry (VBM) is an automated neuroimaging method that is widely used to investigate the brain's structural anatomy to ascertain abnormalities in patient groups for an array of neurological and psychiatric disorders (Ashburner & Friston, 2000; Whitwell, 2009). Broadly, the pipeline for VBM includes segmentation, spatial normalization, modulation, smoothing and statistical analysis.

2.1.1 Segmentation

The pre-processing steps for VBM begin with segmentation and requires the use of T1-weighted images from MRI data. This step separates gray matter, white matter and cerebrospinal fluid (CSF) from each other by measuring their voxel intensities (Ashburner & Friston, 2000). See Figure 1.

2.1.2 Spatial Normalization, Modulation and Smoothing

One hurdle that researchers must overcome in their analyses is the challenge that brain sizes and shapes differ among individuals. To account for these differences VBM includes a non-linear spatial normalization step to register each brain to a template utilizing a 12-parameter affine transformation (Ashburner & Friston, 2000; Whitwell, 2009). The template can be from one subject's image, from an average of all the subjects or most commonly, the Montreal Neurological Institute (MNI) template. Spatial normalization allows all images to be in the same stereotaxic space, providing better accuracy in detecting differences among participants (Ashburner & Friston, 2000). To account for changes in volume from

normalization, modulation can be applied to maintain the local volumes from the original T1-weighted images (Radua et al., 2014; Ridgway et al., 2008; Whitwell, 2009).

Before statistical analyses can be carried out, the data must be smoothed using a Gaussian full width at half maximum (FWHM) kernel so that it is normally distributed and variance across subjects is reduced (Whitwell, 2009). Smoothing involves changing the intensity of each voxel with the average of neighboring voxels (Whitwell, 2009). The amount of intensity change is determined by the chosen kernel, with a lower kernel typically being better appropriate for images that are more accurately aligned and need less correction for misalignment (Ashburner, 2010; Henley et al., 2010). Additionally, sample size and statistical threshold should be taken into account when deciding the smoothing kernel (Shen & Sterr, 2013).

2.1.3 Statistical Analysis

VBM utilizes the general linear model (GLM) to carry out statistical analyses on gray or white matter concentrations (Ashburner & Friston, 2000). This allows for multiple research questions to be explored using standard parametric statistical tests. Parametric tests assume that the data is normally distributed, which is why smoothing is crucial for carrying out the statistical analysis. Additionally, it is important to correct for multiple comparisons, as the analysis includes statistical tests for each voxel (Ashburner & Friston, 2000). The final results from the analysis create statistical maps showing significant voxels.

2.1.4 VBM Limitations

While VBM is automated and simple to use, it is important to note the problems that could arise using the method. For example, there could be issues with misclassification during the segmentation of gray matter, white matter and CSF. Normalization allows for group comparisons, aiming to resolve brain shaped differences by registering the images to a single

template (Karas et al., 2003; Scarpazza & De Simone, 2016). However, it has been previously noted that anatomical variability across subjects, particularly with clinical patients, can cause problems with the accuracy of the registration to a template (Focke et al., 2014; Mechelli et al., 2005; Tisserand et al., 2004). Lastly, the data needs to be normally distributed, which is what the smoothing step does. Applying a smoothing kernel that is too low or high for the sample can reduce spatial resolution and affect the statistical analysis.

2.2 VBM Studies in Gambling Disorder

While the literature for structural neuroimaging in GD is scant, a few studies have explored the topic using VBM methods (Table 1). Nearly half the studies utilizing this method have found no global and/or regional differences between groups. Others have commonly found gray matter reductions in frontal brain regions.

Recently, Freinhofer and colleagues (2020) found no differences in gray matter volume between GD patients and HC. Previous studies focused on exploring whole-brain gray matter volume differences between GD patients and HC found no differences as well (Joutsa et al., 2011; van Holst et al., 2012; Yip et al., 2018). In a ROI analysis of subcortical volumes, there were no group differences between HC and a group containing both at-risk gamblers and GD patients (Grant et al., 2019). Contradictorily, Zois and colleagues (2017) did find significant gray matter reduction in the left superior medial frontal gyrus and medial orbital frontal gyrus between GD patients and HC. Interestingly, Koehler and colleagues (2015) also found differences in the right and left medial frontal gyri, however, their results show increased volume. Additionally, they found increased volume in the right subcallosal gyrus and left inferior frontal gyrus (Koehler et al., 2015). Revealing further conflicting evidence, one study found reduced gray matter volume in the dorsomedial PFC (dmPFC) (Ruiz de Lara et al., 2018). Another found reduced gray matter in the right anterior cingulate cortex (ACC), OFC, precentral gyrus, insula, hippocampus, bilateral putamen and supplemental motor area

(Mohammadi et al., 2016). Draps and colleagues (2020) also found reduced volume in the frontopolar cortex, but in the left hemisphere. An investigation into the neuroanatomical abnormalities of Parkinson's disease (PD) patients with GD found reduced gray matter volume in the left OFC compared to PD patients without GD (Cerasa et al., 2014). They did not find significant differences in the PD group that did not have GD. In a study that split the GD group by low loss- and high loss- aversion measures, gray matter volume reductions in the supramarginal gyrus (SMG) and bilateral posterior cerebellum compared with HC were found (Takeuchi et al., 2017).

These inconsistencies may be due to a few reasons. For one, MRI scanners differ among studies and sample size vary widely, from 24-158 subjects. The study with the largest sample found gray matter reductions in the medial and orbital frontal gyri (Zois et al., 2017). The statistical threshold used is not consistent, with some studies reporting uncorrected results (Table 1). Although all studies utilized VBM, processing pipelines and software are not exactly the same either. Additionally, the heterogeneity of GD patients may cause differences depending on the severity of their symptoms, comorbidities they may suffer or whether they are in treatment.

Table 1. Summary of reviewed sources for VBM in Gambling Disorder

Study	Sample Size GD/Controls (total)	Software	Statistical Threshold	GD vs HC Volume Differences
Joutsa et al. (2011)	12/12 (24)	SPM8	Global Volumes: p<0.05; voxel-level Regional Volumes: p<0.001, uncorrected; voxel-level	No GM/WM global or regional volume differences
van Holst et al. (2012)	40/54 (94)	SPM8	FDR, p<0.05, voxel-level	No GM volume differences
Cerasa et al. (2014)	11***/20 (31)	SPM8	FWE, p<0.05	GD < HC: -left OFC
Koehler et al. (2015)	20/21 (41)	SPM8	p<0.001, uncorrected, voxel-level	GD > HC: -bilateral medial frontal gyrus -right subcallosal gyrus -left inferior frontal gyrus

Study	Sample Size GD/Controls (total)	Software	Statistical Threshold	GD vs HC Volume Differences
Mohammadi et al. (2016)	15/15 (30)	FSL-VBM	FWE, p<0.05, TFCE	GD < HC: -right ACC -right OFC -right precentral gyrus -right insula -right hippocampus -bilateral putamen -supplemental motor area
Takeuchi et al. (2017)	36/36 (72)	SPM12	p<0.005, uncorrected, voxel level; cluster threshold= 200	GD < HC: -supramarginal gyrus -bilateral posterior cerebellum
Zois et al. (2017)	60**/98 (158)	SPM8	p<0.01, voxel level; cluster threshold= 2302	GD < HC: -left superior medial frontal gyrus -right medial orbital frontal gyrus
Ruiz de Lara et al. (2018)	25/25 (50)	SPM8	p<0.001, voxel level; cluster threshold= 416	GD < HC: -dmPFC
Yip et al. (2018)	35/37 (72)	FSL-VBM	FWE, p<0.05, cluster level	No GM volume differences
Grant et al. (2019)	32*/22 (54)	FSL-VBM	FDR, p<0.05, TFCE	No GM/WM volume differences
Draps et al. (2020)	26/25 (51)	SPM12	p<0.001, uncorrected, voxel level; FWE, p<0.05, cluster level	GD < HC: -left frontopolar cortex
Freinhofer et al. (2020)	28/23 (51)	SPM12 CAT12	FWE, p<0.05, voxel level	No GM volume differences

*14 participants were classified at-risk gamblers
**Study also included 47 patients with comorbidities that were not included in review
*** Parkinson's Disease with GD
TFCE= Threshold-free cluster enhancement

2.3 Other Structural Neuroimaging Studies in Gambling Disorders

Briefly, I will go over results from other structural neuroimaging analysis methods to further illustrate the discrepancies in the literature. Using an a priori hypothesis, Rahman and colleagues (2014) used the analysis tool FreeSurfer to investigate hippocampal and amygdala volumes in GD patients compared with HC. They found that the GD group had reduced volumes in both structures. In another FreeSurfer study, researchers did not find whole-brain volume differences, but did find reduced regional volumes in GD patients in the left putamen, right hippocampus and right thalamus (Fuentes et al., 2015). However, it should be noted that this study used a liberal threshold set at 0.01 (uncorrected) for their regional analysis. A recent FreeSurfer study found increased volume in the right inferior frontal gyrus of the GD group

(Irizar et al., 2020). Like the VBM studies, these analyses also point to a disparate and inconclusive theme in the field.

2.4 VBM Studies in Other Addiction Disorders

To provide a comparison of GD to other addiction disorders, I will go over a handful of VBM studies carried out on traditional drug addictions, as well as other behavioral addictions, to present a representation of the literature (Tables 2-3). It is important to note that SUDs have the added complication of pharmacological interference and it is a challenge to differentiate the brain abnormalities caused by the substance from the potential intrinsic abnormalities of having addictive tendencies. This is why behavioral addictions provide an opportunity for investigating addictions without the influence of drugs, which may shed light into its pathophysiology.

2.4.1 Substance Use Addiction

Research focused on traditional substance use addictions typically see reductions in gray matter, particularly in the PFC and subcortical structures, but white matter changes are microscopic and difficult to find (Suckling & Nestor, 2017). Barrós-Loscertales and colleagues (2011) found reduced gray matter volumes in the left striatum and right supramarginal gyrus among patients with CUD. In a meta-analysis investigating regional gray matter abnormalities in AUD, the PFC, dorsal striatum, insula and posterior cingulate cortex were found to have reduced volumes (Table 3) (Xiao et al., 2015). An earlier study also looking into AUD observed significantly reduced gray matter volumes in many regions including areas of the thalamus, hippocampus, cerebellum, precentral gyrus and medial frontal gyrus (Mechtcheriakov et al., 2007). They also found white matter changes in the periventricular regions, pons and cerebellar pedunculi (Mechtcheriakov et al., 2007). Another meta-analysis that explored stimulant drug dependence found significant reductions of gray

matter in the ventromedial prefrontal cortex (vmPFC), insula, inferior frontal gyrus, anterior thalamus and anterior cingulate gyrus (Ersche et al., 2013). The conclusions from Liu and colleagues (2009) investigation of gray matter structure in heroin dependence were decreased volume in the right PFC, left supplementary motor cortex and bilateral cingulate cortex. One unique study that investigated the effects of dependence on betel quid, a psychoactive concoction of areca nut, betel leaf and tobacco that is used by over 600 million people in the world, found reduced gray matter volumes in the midbrain, right- anterior cingulate cortex, superior temporal gyrus and bilateral dlPFC (Chen et al., 2015). Unlike the majority of other studies, Chen and colleagues (2015) found increased volumes in the right- hippocampus and precuneus. Lastly, a whole-brain analysis on polysubstance use disorder observed reduced gray matter in brain regions of the bilateral temporal lobes, thalamus, ACC, cerebellum and occipital lobes (Noyan et al., 2016).

2.4.2 Behavioral Addictions

Other behavioral addiction gaining attention alongside GD are internet gaming disorder (IGD) or internet addiction disorder (IAD). Individuals with IGD face serious psychosocial problems, which poses great threats in a time when online gaming is readily available and heavily marketed towards children and adolescents (Seok & Sohn, 2018). In order to understand the disorder better, Seok and Sohn (2018) conducted a VBM analysis to compare IGD patients and HC, finding IGD patients had reduced gray matter volumes in the bilateral medial frontal cortex. In another IGD study, researchers found gray matter reductions in the OFC, insula and supplementary motor area (Weng et al., 2013). Additionally, their analysis found increased volumes in the left caudate nucleus. Meanwhile, researchers focused in IAD found reduced gray matter in the bilateral dlPFC, OFC, supplementary motor area, cerebellum and left ACC (Yuan et al., 2011). Like GD and SUDs, other behavioral addictions do not have an absolute consensus on which regions are implicated.

2.4.3 Comparing Substance Use Disorders and Behavioral Addictions

Unlike VBM studies in GD, those focused on SUDs have consistently found gray matter differences between patients and HC. To illustrate this point, a few studies include GD patients, SUD patients and HC in their analyses (Tables 1-3). In their study that investigates gray matter integrity in drug and behavioral addictions, Yip and colleagues (2018) did not find differences when comparing GD patients to HC, but did find differences in their patients with cocaine-use disorder (CUD) in regions of the left inferior frontal gyrus, insula and dorsolateral PFC (dlPFC), demonstrating reduced gray matter volume. In their comparisons between CUD and GD patients, they found reduced gray matter volume in the ACC, OFC and medial frontal cortex of the CUD group. Another multi-disorder comparison study focused on GD and alcohol-used disorder (AUD) found no differences between the GD and HC groups, GD and AUD groups, but did find that AUD patients had reduced gray matter volumes in the left frontal cortex, precentral cortex, thalamus and right insula, putamen and supramarginal cortex compared to HC (van Holst et al., 2012). Zois and colleagues (2017) compared HC with three groups of GD patients: 1) GD patients without comorbidities 2) GD patients with AUD and 3) GD with polysubstance use disorder. Contrary to the previous multi-disorder studies, this study did find gray matter differences between HC and GD patients (Table 1). Furthermore, in comparisons with HC, they found GD patients had significantly reduced gray matter volumes regardless of their group. These regions include parts of the PFC, ACC, temporal gyrus, calcarine, and occipital lobe. However, the GD group with AUD also exhibited increased volume in the amygdala and fusiform. In their GD group comparison excluding HC, the GD groups with SUDs had reduced gray matter compared to the GD group without comorbidities in the precuneus and postcentral gyrus. It may be possible that these gray matter reductions in SUDs are more detectable due to the pharmacological component of the disorders which chemically alter the brain to promote addiction behaviors.

When comparing GD to other behavioral addictions, regions that were similarly implicated following VBM analyses were the: PFC, ACC, OFC, insula, supplementary motor cortex and cerebellum (Tables 1-3). From the VBM studies on SUDs these regions were also implicated. Additionally, GD and SUDs shared differences in the putamen, supramarginal gyrus and hippocampus. Although there were other brain regions found to exhibit abnormalities in SUDs, GD and other behavioral addictions which were not shared between them, there is evidence that suggests similar structural abnormalities in areas of the frontal lobe in particular.

Table 2. Summary of reviewed sources for VBM in other addiction disorders

Study	Disorder(s)	Sample Size Patient/HC (total)	Patient (P) vs HC Volume Differences
Mechtcheriakov et al. (2007)	Alcohol use disorder	22/22 (44)	P < HC: GM: -thalamus -hippocampus -cerebellum -precentral gyrus -medial frontal gyrus WM: -pons -cerebellar pedunculi
Liu et al. (2009)	Heroin dependence	15/15 (30)	P < HC: -right PFC -left supplementary motor cortex -bilateral cingulate cortex
Barrós-Loscertales et al. (2011)	Cocaine use disorder Gambling disorder*	20/16 (36)	P < HC: -left striatum -supramarginal gyrus
Yuan et al. (2011)	Internet addiction disorder	18/18 (36)	P < HC: -OFC -left ACC -bilateral dlPFC -cerebellum -supplementary motor area
van Holst et al. (2012)	Alcohol use disorder Gambling disorder*	36/54 (90)	<u>Alcohol use disorder</u> P < HC: -left frontal cortex -left precentral cortex -left thalamus -right insula -right putamen

Study	Disorder(s)	Sample Size Patient/HC (total)	Patient (P) vs HC Volume Differences
			-right supramarginal cortex Group Comparisons CUD vs GD: No differences
Weng et al. (2013)	Internet gaming disorder	17/17 (34)	P < HC: -OFC -insula -supplementary motor area
Chen et al. (2015)	Betel quid dependence	33/32 (54)	P < HC: -right anterior cingulate cortex -right superior temporal gyrus -bilateral dlPFC
Noyan et al. (2016)	Polysubstance use disorder	46/30 (76)	P < HC: -ACC -thalamus -cerebellum -occipital lobes -bilateral temporal lobes
Zois et al. (2017)	Gambling disorder w/ SUD (AUD and polysubstance use disorder) Gambling disorder w/o SUD*	47/98 60/98 (205)	Gambling disorder w/ SUD P < HC -PFC -ACC -temporal gyrus -calcarine -occipital lobe P > HC (AUD only) -amygdala -fusiform Group Comparisons GD w/o SUD > GD w/ SUD -precuneus -postcentral gyrus
Yip et al. (2018)	Cocaine use disorder Gambling disorder*	37/37 35/37 (109)	Cocaine use disorder P < HC: -insula -dlPFC -left inferior frontal gyrus Group Comparisons CUD < GD: -ACC -OFC -medial frontal cortex
Seok & Sohn (2018)	Internet gaming disorder	20/20 (40)	P < HC: -bilateral medial frontal cortex

*see table 1 for results

Table 3. Summary of meta-analysis sources for VBM in other addiction disorders

Study	Disorder	Sample Size Patient/HC (total)	Patient (P) vs HC Volume Differences
Ersche et al. (2013)	Stimulant drug dependence	494/428 (922)*	P < HC: -insula -vmPFC -anterior thalamus -inferior frontal gyrus -anterior cingulate gyrus
Xiao et al. (2015)	Alcohol use disorder	296/359 (655)**	P < HC: -PFC -insula -dorsal striatum -posterior cingulate cortex

*Participants from 14 studies included in meta-analysis
**Participants from nine studies included in meta-analysis

2.5 VBM and the Cognitive Features of Gambling Disorder and Addiction

2.5.1 VBM Studies and Impulsivity

Impulsivity is considered a multi-dimensional trait which is characterized by hurried and maladaptive decision making that is carried out without thoughtful planning or consideration of consequences (Clark, 2014). Studies have shown that individuals with GD present with higher impulsivity measures and behavior compared with HC (Ioannidis et al., 2019; Mestre-Bach et al., 2020). The primary brain region implicated in impulsivity is the frontal lobe, an area that is regarded as the center for higher-level cognitive and executive functioning. It is thought that the frontal lobe plays a vital role in decision-making by integrating past experiences with knowledge of potential consequences (Crews & Boettiger, 2009; Mackey et al., 2017; Qiu et al., 2013). Specifically, the dlPFC, ACC and OFC are involved in these processes as they project to the ventral striatum to create a cooperative relationship with deep brain structures to maintain appropriate decision-making abilities (Crews & Boettiger, 2009). This suggests that when the decision-making system is functioning abnormally, impulsive behaviors may become pervasive as the system is unable to support inhibition.

Using VBM, Matsuo and colleagues (2009) investigated the possible correlation between brain matter and impulsivity in healthy participants, finding subjects with high impulsivity had smaller gray matter volumes in the OFC and ACC. In a similar morphometric correlational study, the medial PFC, ACC and OFC were found to share a negative correlation with impulsivity scores (Cho et al., 2013). In the same study, a positive correlation was found between impulsivity scores and regional brain sizes of the superior temporal gyrus and parahippocampal gyrus. Freinhofer and colleagues (2020) found no correlations between offers of "smaller but sooner" (SBS) rewards and gray matter volume in GD patients, but did find a negative correlation with HC in the left medial orbital gyrus. They suggest that higher gray matter volume is associated with lower impulsivity. Findings from a study looking into the structural correlates of impulsivity in IGD found a correlation between impulsivity and the left fusiform gyrus, right- dmPFC, amygdala and bilateral insula and OFC (Du et al., 2016). Supporting these findings, an investigation into heroin-dependent individuals found they had decreased gray matter volumes compared to HC in regions of the right fusiform gyrus and bilateral- medial PFC and dlPFC, which also corresponded to higher impulsivity scores (Qiu et al., 2013).

2.5.2 VBM Studies and Compulsivity

Alongside impulsivity is the compulsive aspect of GD. Often confused with each another, compulsivity refers to repetitive, habitual actions that are carried out to prevent a perceived negative consequence even if the actions themselves lead to negative consequences (Mallorquí-Bagué et al., 2018). It has been postulated that the progression into addiction begins with impulsive behavior which later shifts into more compulsive behavior, believed to occur from motivational changes (van Timmeren et al., 2018). In addition, habit learning has been proposed to be a feature of compulsivity. Habits are automatic behaviors that form from goal-directed systems and associative learning to allow us to react automatically or without

much planning and cognitive effort (Fineberg et al., 2014; Gillan et al., 2016). It is thought that a habit's role in compulsivity occurs when individuals no longer utilize their goal-oriented behavior, which requires continual learning, and instead rely on their habits, even in the face of repeated exposure to negative outcomes (Fineberg et al., 2014). This may explain why GD patients continue to gamble even when they experience continued losses and psychological distress.

The literature focused investigating brain regions associated with compulsivity is limited. In one study that includes multiple pathological compulsive disorders, the OFC and ventral striatal volume were decreased and researchers suggest that these regions are associated with habit formation (Voon et al., 2015). Montigny and colleagues (2013) also found that reduced volumes in the OFC, ventral striatum and dlPFC correlated with compulsive behavior in their research with multiple compulsive disorders. In their study on compulsivity in alcohol dependence, Grodin and colleagues (2017) found patients with AUD had smaller anterior insula and cingulate volumes, which were negatively correlated with compulsivity measures.

3 Aims of the Present Thesis

The primary goal of this thesis is to investigate whether there are structural abnormalities in individuals with gambling disorder by performing an exploratory analysis into global- and regional- gray and white matter volumes. I hypothesize that compared to HC the GD group will display 1) whole-brain volume without atrophy and 2) reductions in regional volumes in brain areas related decision-making, cognitive functioning and reward processing such as the frontal lobe and ventral striatum.

4 Materials and Methods

4.1 Materials

4.1.1 Participants

The subjects include 15 individuals diagnosed with GD (formerly known as PG) and 17 healthy controls (N= 32). Healthy controls were age-, sex- and weight- matched to GD patients in order to control for variability. Recruitment consisted of advertising in local Finnish newspapers and on websites related to gambling. Inclusion criteria for the GD group included a diagnosis of PG according to the DSM-IV and a lack of diagnosis and relevant PG symptoms for HC. PG diagnoses were confirmed in a clinical interview. For both groups, exclusion criteria included: other DSM-IV diagnosis, serious medical problems or disease, alcohol and/or substance use dependence within the past 6 months, recent intoxication from alcohol or drugs, body weight < 180kg, current pregnancy, inability to undergo MRI and coffee/tea consumption 12 hours before the study. All subjects completed clinical interviews, blood samples, the South Oaks Gambling Screening (SOGS) and Alcohol Use Disorders Identification Test (AUDIT) (Majuri, 2019). Descriptive statistics were reported for participant demographics using Mann-Whitney U and chi-square tests with a significance at $p<0.05$ in order to compare the groups (Table 4).

4.1.2 MRI Acquisition

Structural MRI was performed using a 3.0T Philips Ingenuity scanner (Philips Healthcare, Cleveland, OH, USA). Both a 34-channel receiving head coil and a sagittal 3DT1-weighted TFE sense pulse sequence (TR 8.1 ms, TE 3.7 ms, flip angle 7°, matrix 256 × 256, 176 slices) were used with an isotropic voxel (Majuri et al., 2017).

4.2 Methods

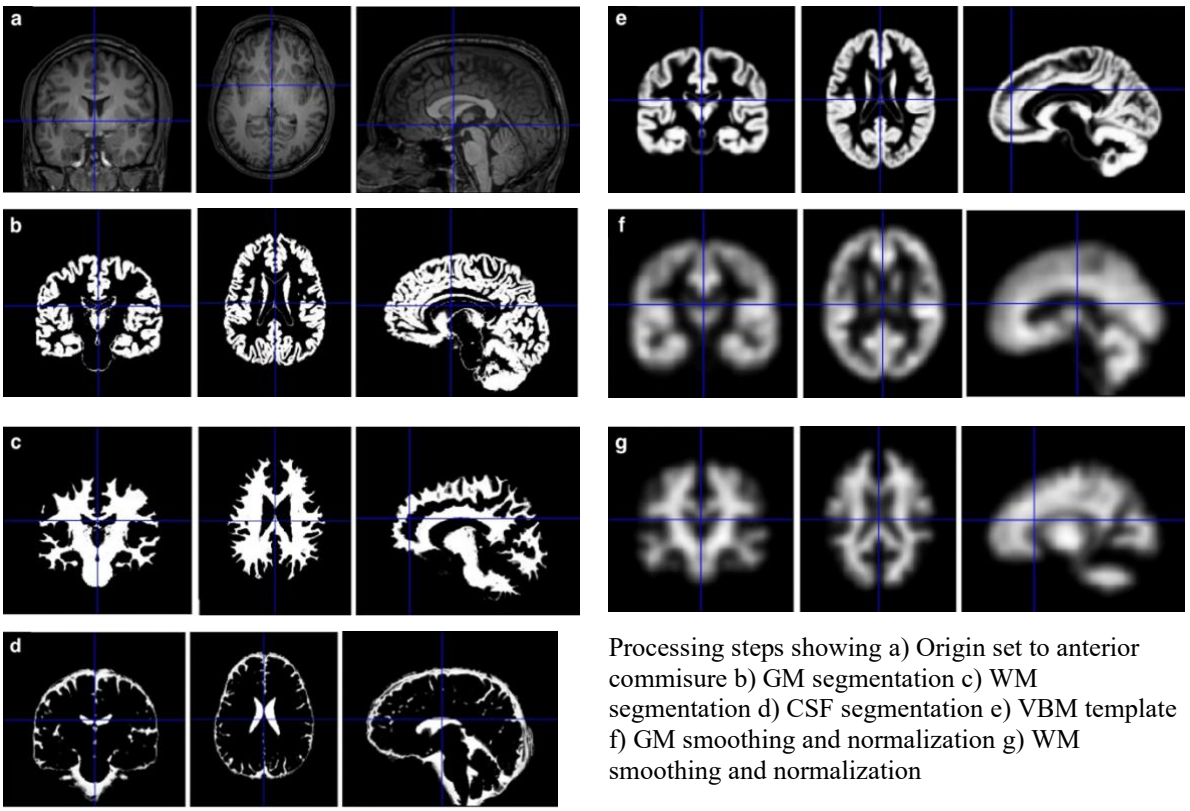
4.2.1 VBM: Pre-processing and Statistical Analysis

Voxel-based morphometry (VBM) is a tool used to make voxel-by-voxel comparisons of local brain tissue intensities. (Ashburner & Friston, 2000). The analysis pipeline includes segmenting gray matter, white matter and CSF and normalizing, modulating and smoothing the brain images to allow for statistical tests (Figure 1). It is possible to not perform modulation, which will instead analyze concentration differences of brain matter rather than an absolute amount or volume of brain matter (Matsuda, 2013). Statistical parametric mapping (SPM) is one software option to carry out VBM analysis. I will be performing the VBM analysis using SPM8 (The Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion. ucl.ac.uk/spm). This is an older version of SPM, however, we will be comparing results to our group's earlier study that used the VBM8 toolbox.

The anterior commissure was set as the origin for each T1-weighted image before segmenting the images to gray matter, white matter and CSF. Visual inspection was carried out to check for tissue misclassification. This study used the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) option which creates a template that is specific to the study group by taking individual images and matching them to an average template to create a new template through multiple iterations (Michael et al., 2016). This method has been shown to be more precise in inter-subject registration than the standard pipeline and was used to maximize possible differences between groups (Henley et al., 2010; Lin et al., 2013). The DARTEL template was then used to spatially normalize the individual data to MNI space. Modulation was selected to preserve volume amounts. A smoothing kernel of 8-mm Gaussian full width and half maximum (FWHM) was chosen because using DARTEL should allow for better registration, so a higher kernel would not be appropriate. For comparison, a 10-mm Gaussian FWHM smoothing kernel was also looked at. For the

whole-brain analysis, an independent sample's t-test was carried out to compare global volumes (Table 5). For the regional analysis, a GLM was set to compare the GD group with HC for both gray and white matter differences, controlling for age and total intracranial volume (TIV). TIV was calculated by extracting gray matter, white matter and CSF volumes from the modulated images and adding them together. Additionally, a threshold masking of 0.1 was used in order to exclude non-brain regions. The significance threshold was set at $p<0.05$ with family-wise error (FWE) corrections. A less conservative threshold of $p<0.001$ (uncorrected) with an extent threshold set at $k=50$ to further minimize false positives was also looked at to explore potential effects. Post-hoc correlational analyses were conducted on SPSS software (IBM Corp., version 27.0, Armonk, N.Y., USA) between SOGS scores, problematic gambling years and brain volumes.

Figure 1. VBM pre-processing pipeline



Processing steps showing a) Origin set to anterior commisure b) GM segmentation c) WM segmentation d) CSF segmentation e) VBM template f) GM smoothing and normalization g) WM smoothing and normalization

5 Results

5.1 Psychometric Data

Participant characteristics can be found in table 4. There were no significant differences between groups in age, gender, weight, smoker status and AUDIT scores. As expected, there were differences between groups in gambling hours, gambling spending, problem gambling years and SOGS scores ($p<0.05$).

Table 4. Demographic and Clinical Characteristics of Participants

Variables	Gambling Disorder (n=15)	Control (n=17)	p-value
Age (years)			
Mean (SD)	42.6 (11.8)	43.3 (11.1)	0.73†
Min-Max	24-66	24-58	
Gender			
Female/Male	8/7	9/8	0.98‡
Weight (kg)			
Mean (SD)	74.6 (13.2)	73.6 (7.1)	0.98†
Min-Max	55-107.5	58-85	
Smoker Status			
Yes/No	11/4	7/10	0.07‡
Gambling Hours (weekly)			
Mean (SD)	8.9 (7.1)	0.5 (1.2)	<.00001†
Min-Max	1-20	0-5	
Gambling Spending (euros/week)			
Mean (SD)	163.6* (147.5)	3.94 (7.4)	<.00001†
Min-Max	10-500	0-30	
Problem Gambling (years)			
Mean (SD)	11.6 (7.3)	0	<.00001†
Min-Max	1-24	0	
SOGS Score			
Mean (SD)	13.3 (2.3)	(0.3)	<.00001†
Min-Max	10-16	0-1	
AUDIT Score			
Mean (SD)	5.9 (4.0)	5.4 (3.3)	0.62†
Min-Max	0-15	1-12	

† Mann-Whitney U Test
‡ Chi-square test
* Spending information for one participant was not available

5.2 Inter-Subject Registration in VBM8

The original T1-weighted images of the subjects show visible differences in brain shape and size between subjects (Figure 2A). The final DARTEL template that was created for normalization was iterated six times and depicts more closely aligned images (Figure 2B). The template and output flow fields were used to spatially normalize the individual tissue data to MNI space so that variance between subjects is minimal (Figure 2C and 2D).

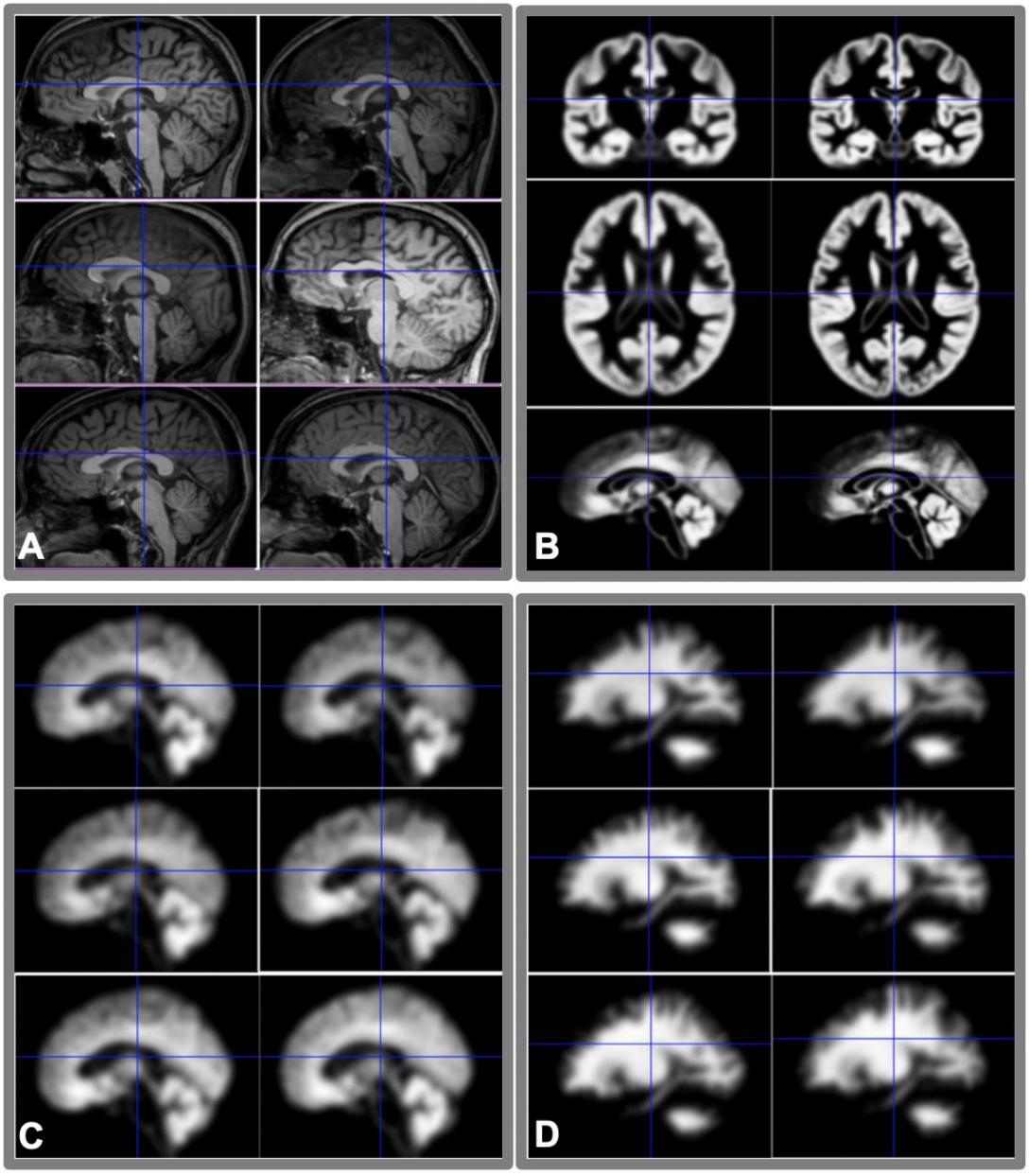


Figure 2. Inter-subject registration is used in VBM8 to place all subjects into the same stereotaxic space. Requires the input of A) T1-weighted images (six participants shown), B) DARTEL template; first iteration template (left) and final iteration template (right), to output modulated, smoothed and normalized C) gray matter and D) white matter and CSF (not pictured).

5.3 Whole-Brain Volume

The independent samples t-test to compare whole-brain volumes found no significant differences between the GD group and HC in regard to total gray matter-, white matter- and total brain- volumes (Table 5 and Figure 3).

Table 5. VBM results for whole-brain volume analysis

Volume	Gambling Disorder, cm3	Control, cm3	t	p-value
Gray Matter Volume	741.77±70.75	725.66±90.85	-0.554	0.584
White Matter Volume	441.23±40.40	423.36±46.24	-1.157	0.256
Total Brain Volume	1433.18±146.29	1414.58±162.57	-0.338	0.736

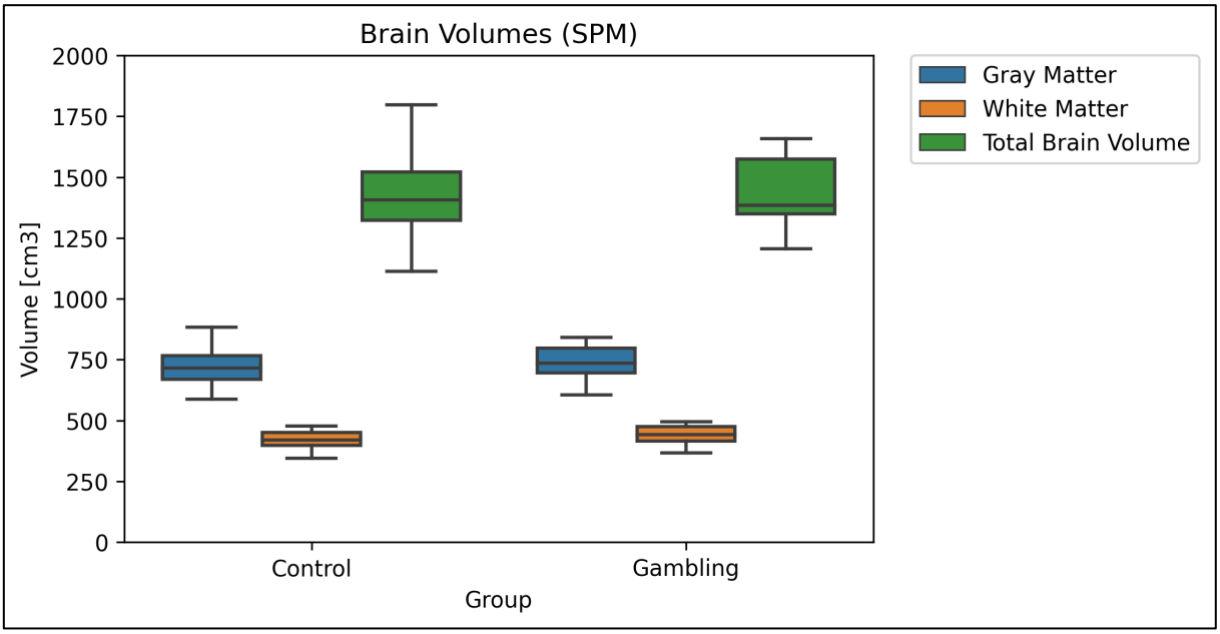


Figure 3. Boxplot showing VBM whole-brain volume results for gray matter, white matter and total brain volumes.

5.4 Regional Brain Volume

Comparisons of regional brain volumes yielded no differences in gray or white matter volumes between the GD group and HC after correcting for multiple. These results did not change when using a 10-mm Gaussian FWHM kernel smoothing. An exploration using a less strict statistical threshold ($p<0.001$, uncorrected) found decreased volume between groups in the left superior temporal gyrus, right parahippocampus and somatosensory cortex (Table 6).

Higher volumes in the left dlPFC and occipital lobe were detected in the GD group. White matter differences were found in the frontal lobe (Table 7).

Table 6. VBM Results for regional gray matter volume analysis

Shows regions where GD gray matter volume is less/more than HC at p<0.001, uncorrected, k=50

Region	Laterality	Effect	MNI Coordinates X Y Z	z-score	Cluster Size
Superior Temporal Gyrus	Left	GD < HC	-54 -16 -6	4.10	75
Region outside brain			11 69 -21	3.72	70
Region outside brain			12 -13 -38	3.64	81
Right Parahippocampus	Right	GD < HC	24 0 -36	3.64	103
Region outside brain			26 18 -50	3.48	79
Somatosensory Cortex	Right	GD < HC	14 9 37	3.45	150
dlPFC	Left	GD > HC	-18 50 30	4.25	165
Occipital Lobe	Left	GD > HC	-8 -85 44	3.83	64

Table 7. VBM Results for regional white matter volume analysis

Shows regions where GD white matter volume is less/more than HC at p<0.001, uncorrected, k=50

Region	Laterality	Effect	MNI Coordinates X Y Z	z-score	Cluster Size
Inferior Frontal Gyrus	Left	GD < HC	-31 38 -6	3.47	55
Frontal Lobe	Left	GD < HC	-21 42 15	3.46	57

5.5 Correlation Analyses

The results from the Pearson's correlation analysis found a significance between SOGS scores and problematic gambling years ($r=0.741$, $p<0.05$). No correlation was found between SOGS scores and gray matter-, white matter- or global- volumes (Figure 3). Additionally, no correlation was found between problem gambling years and brain volumes.

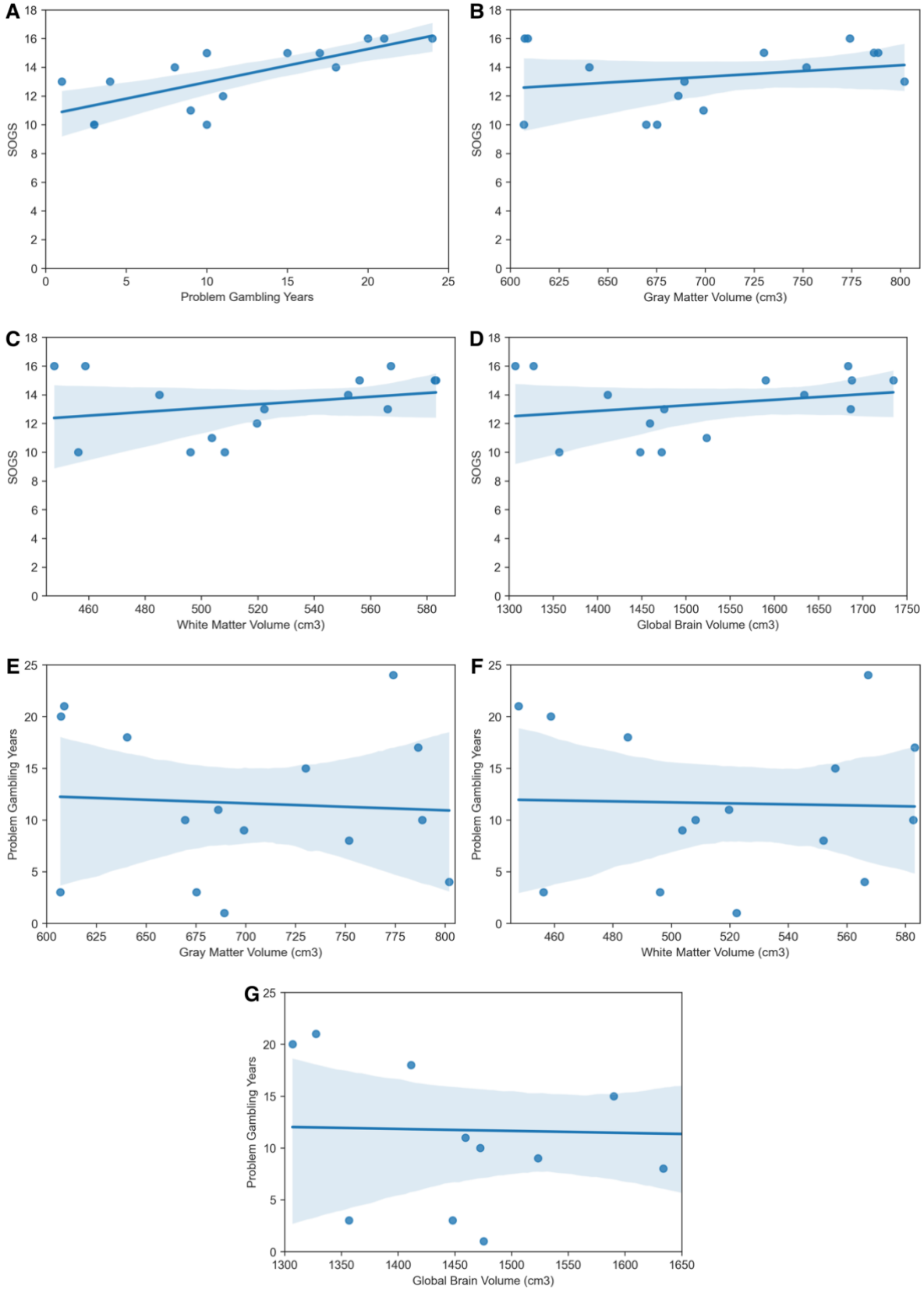


Figure 4. Scatter plots depicting correlational analysis with SOGS scores and A) problematic gambling years, r=0.741, P=0.002, B) gray matter volume, r=0.244, P=0.381, C) white matter volume, r= 0.269, P=0.333, D) global brain volumes, r= 0.243, P= 0.383. Additionally, correlational analysis with problematic gambling years and E) gray matter volume, r= -.064, P=0.820, F) white matter volume, r= -0.034, P= 0.915 G) global brain volumes, r= -0.038, P= 0.894.

6 Discussion

In this study, our goal was to investigate the structural abnormalities in GD using VBM. We hypothesized that there would be no global atrophy present in the GD group, but that there would be regional differences between GD patients and HC. Supporting our first hypothesis, we did not find differences in global volumes between groups. Diverging from our second hypothesis, we found that individuals with GD did not exhibit regional gray or white matter volume abnormalities.

6.1 Absence of Structural Abnormalities in Gambling Disorder

Previous VBM studies are inconclusive regarding the structural differences between GD and HC groups (Table 1). Our findings support previous studies that did not find global and regional volume differences between GD and HC groups (Freinhofer et al., 2020; Grant et al., 2019; van Holst et al., 2012; Yip et al., 2018). Additionally, our result supports prior findings from our group that found no group differences in global and regional brain volumes using VBM8 (Joutsa et al., 2011). However, our previous study did not find differences even when using a less strict threshold ($p<0.001$, uncorrected). In the current study, we had a larger cohort of subjects, which may have lent to improved statistical power to detect differences at this threshold.

It has been postulated that the cognitive impairments associated with problem gambling behavior may give rise to structural abnormalities in GD as they do in SUDs (van Holst et al., 2012). Our findings, which found an absence of structural abnormalities in GD, contrast with this theory. One supposition is that prolonged, chronic substance use causes structural abnormalities, leading to structural abnormalities in SUDs, but not in GD. A second supposition is that structural abnormalities precede SUDs, but not GD. Therefore, it is possible that structural abnormalities relating to tissue volume are not inherent to addiction, as

GD is seen as a prototype for addiction disorders. It may also possible that the cognitive abnormalities found in behavioral addictions manifest in a distinct manner. For example, in our group's previous study with GD patients, an investigation using diffusion tensor imaging (DTI) found lower fractional anisotropy (FA) in brain regions that were also associated in SUD patients (Joutsa et al., 2011). Therefore, microscopic white matter integrity may play a more prominent role in GD's pathophysiology than volumetric changes.

6.2 Exploratory and Correlational Analyses

In an exploration into potential brain volume differences using a less conservative statistical threshold ($p<0.001$, uncorrected), the left superior temporal gyrus, right parahippocampus and somatosensory cortex were found to have less volumes in the GD group. Previously, the superior temporal gyrus has been negatively associated with impulsivity measures (Cho et al., 2013). It is not clear how this region is relevant to impulsivity, as it is traditionally known for its role in auditory and speech processing (Chang et al., 2010). In a study investigating impulsivity and temporal lobe thickness in internet addiction disorder, researchers found that patients exhibited a thinner superior temporal cortex in the left hemisphere (Zsidó et al., 2019). The parahippocampus is involved with memory as it serves as an input to the hippocampus, a region that has been linked to drug-cue associations and altered long-term potentiation (LTP), a vital process that aids in learning (Kutlu & Gould, 2016). Some studies in GD and SUDs have found reduced gray matter volumes in the hippocampus, but not the parahippocampus (Tables 1-3). The postcentral gyrus houses the somatosensory cortex and has been associated with lower brain activation in patients with non-substance addictions and higher brain activation in SUDs (García-García et al., 2014; Wang et al., 2017). Meanwhile, greater volumes in GD patients were found in the dlPFC and occipital lobe, contrasting with previous findings from GD and SUDs that found decreased volume in these regions (Tables 1-3).

White matter differences are less commonly reported using VBM, as other methods like DTI are preferred to accurately find white matter tract abnormalities. In our exploratory analysis, GD patients demonstrated decreased white matter volume in the frontal lobe regions.

Finally, we wanted to investigate the relationship between gambling behavior and brain volume. A post-hoc correlational analysis was carried out to detect relationships between SOGS scores, problem gambling years and brain volumes of the participants with GD (Figure 4). A positive association was made between SOGS scores and problem gambling years. However, our results did not find a relationship between SOGS scores and brain volume or between problem gambling years and brain volume.

6.3 Limitations and Future Research

A major limitation of this study is the small sample size, causing lower statistical power. Second, VBM8 is an older tool and updated toolboxes have been released. One study compared VBM8 to CAT12, a toolbox from the current SPM version (SPM12) on detecting structural abnormalities in individuals with temporal lobe epilepsy (Farokhian et al., 2017). They found that the VBM8 toolbox is less reliable than CAT12 for detecting morphological changes. Included in the SPM12 update were enhancements to spatial processing, and inter-subject registration in particular (The Wellcome Department of Imaging Neuroscience, London, 2014). It has been previously noted that VBM may not perform inter-subject registration well for clinical groups due to large individual variance (Shen & Sterr, 2013). Furthermore, the exploratory, whole-brain focus of the study may have been a limiting factor, as statistical tests are applied to a large amount of voxels (Whitwell, 2009). Perhaps a region of interest (ROI) design is better suited if differences between GD patients and HC are small or concentrated to specific regions.

Future studies should aim to increase sample size to maximize statistical power. This can be done by implementing a multi-site study design or recruiting from addiction clinics.

Using updated or different analysis software like CAT12 or FreeSurfer could be useful in these investigations to reproduce and confirm results. Cognitive tests related to decision-making, impulsivity and other cognitive deficits related to GD and addiction should be carried out during intake for more thorough correlation analyses. Investigations and comparisons with other behavioral addictions may be useful in shedding light on the pathophysiology of addiction. Finally, alternative neuroimaging methods like DTI or PET should be used to investigate possible microscopic differences and neurobiological abnormalities related to transmitters and receptor density levels.

7 Conclusion

Gambling disorder is a psychiatric disorder that causes detrimental effects to one's life, so it is important to understand its etiology. In order to investigate GD's structural integrity a whole-brain analysis was carried out using VBM. The analysis found no significant differences in global- and regional- gray and white matter volumes between GD patients and HC. These findings suggest differences between groups are lacking and GD volume abnormalities are not a reliable biomarker for the disease. This contrasts from findings for SUDs, which reveal regional brain atrophy. Future studies should use larger sample sizes and implement improved methodological tools to maximize findings.

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