

INVESTIGATION OF THE RELATIONSHIP BETWEEN TISSUE
CHARACTERISTICS AND TIME PERCEPTION IN HEALTHY AGING

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ABSTRACT

INVESTIGATION OF THE RELATIONSHIP BETWEEN TISSUE CHARACTERISTICS AND TIME PERCEPTION IN HEALTHY AGING

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Brain ubiquitously receives temporal information. As people get older, their timing performances change. Interval timing requires cognitive resources such as attention, long-term memory, and working memory. Unfortunately, these functions deteriorate with aging. Changes in time perception are reported in healthy aging, as are several different neuropsychiatric disorders. Although age-related changes in time perception have been amply described in the literature, the actual underlying mechanisms remain controversial. This study included a total of 33 young (mean age = 23.31 years) and 33 old (mean age = 67.63 years) individuals who performed a time bisection task with a range of 1.25-2.5 seconds. The young and old participants showed similar time bisection performances ($p \geq 0.05$). The experimental design was strictly controlled to minimize the effects of age-related declines in cognitive functions. Contrary to psychometric measurements, self-rated reports indicated that the impressions of the participants about present time perception differ though aging.

The spin lattice relaxation times (T_1) on entire brain were mapped with an ROI based method. T_1 prolongation with aging was demonstrated on numerous cortical and subcortical area, which was interpreted as increased demyelination in these structures.

Also, the relationship between MRI and behavioral data was investigated: significant correlations between behavioral outcomes and various brain structures including timing circuits such as cerebellum and hippocampus were shown. Finally, regression analyses showed that one of the basic measures of time perception, bisection point, is predicted by the T_1 values of certain subcortical brain areas such as cerebellum, hippocampus and putamen.

Keywords: Aging, Temporal Bisection, Striatum, Spin-Lattice Relaxation Time (T1), Magnetic Resonance Imaging (MRI)

ÖZ

SAĞLIKLI YAŞLANMADA DOKU KARAKTERİSTİKLERİ VE ZAMAN ALGISI İLİŞKİSİNİN İNCELENMESİ

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Beyin her daim zamansal bilgileri alır ve işler. İnsanlar yaşlandıkça zamanlama performansları değişir. Aralıklı zamanlama, dikkat, uzun süreli hafıza ve çalışan hafıza gibi bilişsel kaynaklar gerektirir. Ne yazık ki, bu işlevler yaşlanma ile bozulmaktadır. Zaman algısındaki değişiklikler, birkaç farklı nöropsikiyatrik bozuklukta olduğu gibi, sağlıklı yaşlanmada da rapor edilir. Her ne kadar zaman algısındaki yaşa bağlı değişiklikler literatürde fazlasıyla tanımlanmış olsa da, gerçekten altta yatan mekanizmalar tartışmalıdır. Bu çalışmaya, 1,25-2,5 saniye aralığında süre ayırıştırma görevi yapan 33 genç (ort. Yaş = 23.31) ve 33 yaşlı (ort. Yaş = 67.63) katıldı. Genç ve yaşlı katılımcılar benzer süre ayırıştırma performansları sergilemişlerdir ($p \geq 0,05$). Deney özellikle bilişsel fonksiyonlarda yaşa bağlı düşüşlerin etkilerini en aza indirmek için tasarlandı. Psikometrik ölçümlerin aksine, katılımcıların sözlü ifadelerine bakıldığında genç ve yaşlıların zamanın geçişi hakkındaki izlenimlerinin farklı oldu görüldü.

Tüm beyinde ilgili alanlarda longitudinal relaksasyon süreleri (T_1) haritalanmıştır. Yaşlanma ile T_1 uzaması, bu yapılarda artmış demiyelinizasyon olarak yorumlanan çok sayıda kortikal ve subkortikal alanda gösterilmiştir. Ayrıca, MRG ve davranışsal veriler arasındaki ilişki araştırılmıştır: davranışsal sonuçlar ile beyincik ve

hipokampus gibi zamanlama devreleri dahil olmak üzere çeşitli beyin yapıları arasındaki anlamlı korelasyonlar bulunmuştur. Son olarak, regresyon analizleri, zaman algısının temel ölçümlerinden biri olan biseksiyon noktası, serebellum, hipokampus ve putamen gibi bazı subkortikal beyin alanlarının T_1 değerleri ile tahmin edildiğini göstermiştir.

Anahtar Kelimeler: Yaşlanma, Süre Ayrıştırma, Striatum, Longitudinal Relaksasyon Süresi (T_1), Manyetik Rezonans Görüntüleme (MRG)

I dedicated my thesis to the sun of my life, my beloved son Toprak Diñer

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
BG	Basal Ganglia
BP	Bisection Point
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DAT	Dopamine Transporter Protein
DL	Difference Limen
DLPFC	Dorsolateral Prefrontal Cortex
DTI	Diffusion Tensor Imaging
FA	Flip Angle
FAST	FMRIB's Automated Segmentation Tool
FDRI	Field-Dependent Relaxation Rate Imaging
FLASH	Fast Low Angle Shot
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
GABA	γ -Aminobutyric Acid
GDS	Geriatric Depression Scale
GM	Gray Matter
GRE	Gradient Recalled Echo
IR	Inversion Recovery
LCN	Lateral Cerebellar Nucleus
LL	Look-Locker
MFC	Magnetic Field Correlation
MMSE	Mini-Mental State Examination
MP2RAGE	Magnetization-Prepared 2 Rapid Acquisition Gradient Echoes
MPRAGE	Magnetization Prepared Rapid Gradient Echo

MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
PCA	Principal Component Analysis
PD	Parkinson's disease
PD	Proton Density
PET	Positron Emission Tomography
PSE	Point of Subjective Equality
PVE	Partial Volume Effects
qMRI	Quantitative MRI
R₁	Longitudinal Relaxation Rate
R₂	Transverse Relaxation Rate
REST	Repressor Element 1-Silencing Transcription
ROI	Region of Interest
rTMS	Repetitive Transcranial Magnetic Stimulation
SMA	Supplementary Motor Area
STCA	Scaffolding Theory of Cognitive Aging
SWI	Susceptibility-Weighted Imaging
T₁	Longitudinal Relaxation Time
T₂	Transverse Relaxation Time
TE	Echo Time
TLRC	Talairach-Tourneux Coordinates
TR	Repetition Time
TÜİK	Türkiye İstatistik Kurumu
VFA	Variable Flip Angle
WM	White Matter
WR	Weber Ratio

CHAPTER 1

INTRODUCTION

Timing is a ubiquitous ability of the most of the living organisms; it is the fourth dimension. Behaviors related to judgements in the range of seconds-to-minutes are defined as interval timing performance. We can see numerous examples of interval timing in most of the basic daily routines such as brewing tea, foraging of animals in wild nature (Brunner, Kacelnik, & Gibbon, 1992) or more complex actions like decision making in the case of future reward (Mazur, 1984). The necessity of presenting time is crucial for capturing environmental changes and estimation of predictions about events and consequences. By interpreting these time cues we can make decisions about how to react to these environmental changes.

Interval timing requires usage of cognitive resources related to time perception such as encoding of incoming temporal information, and long-term memory for storage, retrieval and comparison with the reference temporal durations in working memory. This complicated interaction between cognitive functions and interval timing makes time perception a good candidate model of cognitive aging consisting of difficulty in attention allocation, memory decline and related neural substrate alterations.

On the other front, another age-related change occurring in the human brain is tissue characteristics, which can be observed through MR image signal differences. There has been great interest in using MRI to quantify age-related changes in the human brain for a long time. For instance, the spin-lattice (or longitudinal) relaxation time T_1 quantifies the rate of transfer of energy from the nuclear spin system to the neighboring molecules (Liang, 2000). The spin-lattice relaxation time (T_1) of human brain tissue has previously been used as an indicator of brain development or brain maturation (Wahlund, 1990). T_1 provides valuable information about the underlying

tissue microarchitecture since it is affected by myelin and iron concentrations in the brain tissue (Ogg, 1998; Stuber, 2014).

The brain areas involving temporal processing such as caudate, frontal lobes and cortico-striatal circuits were also subject to age-related structural changes. From this point of view, it is worthy to introduce the term “de-generacy” which is a form of compensation corresponding to recovery of neural networks (Edelman & Gally, 2002; Whitacre, 2010).

De-generacy can be defined as the ability of different brain regions or networks to generate same or analogous output instead of impaired or dysfunctional ones (Harrington & Jahanshahi, 2016; Jones & Jahanshahi, 2014). The dysfunctions in timing are probably less pronounced in normal aging due to processes related to de-generacy (Balci, Meck, Moore, & Brunner, 2008; Church et al., 2014). To be able to maintain timing performance, older individuals may activate or recruit alternative networks or cognitive processes especially when they are under cognitive demand or age-related physical decline. Moreover, this could enlighten the paradoxical outcomes of literature on age-related timing performances. In simple timing tasks which minimize cognitive demands, intervention of the alternative networks or processes are unnecessary, therefore age differences are subtle or absent. On the other hand, if the task is cognitively demanding, age-related differences are more obvious and eventually the ability of the elderly to compensate becomes inadequate (Turgeon et al., 2016).

Taken together with the de-generacy perspective, the relationship between timing performances and the T_1 relaxation time might provide a good explanation to the time perception processes across ages.

In this study, we mainly investigated the relationship between time bisection performances of young and old individuals on supra-second range and the structural changes of T_1 maps on the whole brain. For this purpose, we collected behavioral data

in the time bisection task and structural data in terms of T_1 longitudinal relaxation time characteristics.

Chapter 2 covers the literature review. It handles the structural changes in aging brain and then introduces qMRI method and its importance in aging studies. Afterwards, cognitive changes observed in aging process are presented with an emphasis on time perception.

Motivation and the hypotheses of the thesis are given in Chapter 3. Experimental design of the behavioral experiments and the acquisition, pre- and post-processing steps of the MRI data are given in Chapter 4. Chapter 5 is composed of the results of the analyses. Outcomes are discussed in Chapter 6. Finally, concluding remarks and future directions are presented in Chapter 7.

CHAPTER 2

BACKGROUND

'Age is an issue of mind over matter. If you don't mind it doesn't matter'

Mark Twain

The Greek philosopher Hesiod divided the history of humankind into five epochs. The Age of Gold, the time of Cronus (or Chronos), was the first one in which nature gave everything to humans by itself. Peace and happiness were common and humans never aged, even immortal. The Age of Silver came later, in that childhood continued about a hundred years with a short-term adulthood. The Bronze Age was the third epoch, the age that Hesiod lived in. This time was dominated by violence, greed and lack of justice. After this age Heroic Age was created by Zeus and demigods were lived in the world. Finally, our age emerged: The Iron Age. According to the predictions of Hesiod, this age would be composed of violence, self-seeking and getting worse lifestyle. He also predicted that Zeus would create a new and idealized age.

Like Hesiod, we dream about a 'Golden Age' that we would all live peacefully, in eternal youthfulness, at least a better quality of living and aging like a fine wine. In addition to this, we have really strong scientific foundations. The tools of modern biology might help unveil the underpinnings of aging and even control it.

Aging in Numbers

According to the 2017 Revision of the World Population Prospects, older persons aged over 60 are estimated to account for 13 % of the world's population (962 million) as of mid-2017 (Unidas., 2017). Future fertility ratios determine the future population growth. The world population is aging as a consequence of decreasing birth rate and

increasing of life expectancy. Globally the projections of life expectancy at birth increased from 71 years in 2010-2015 to 77 years in 2045-2050. The growth rate of the population aged 60 or over in the world is about 3 % per year. At present, the greatest proportion of the population aged 60 or over (25 % of total population) is in Europe. The other parts of the world will follow to this fast aging process, in such a way that all regions (except Africa) will almost have a quarter or more people aged over 60 by 2050.

According to Turkish Statistical Institute's report on population, older individuals aged 65 or over increased by 16 % in 2018 compared to 2014 (Türkiye İstatistik Kurumu (TUİK), 2018). The percentage of older people was 8 % of the total population in 2014 and this percentage increased to 8.8 % by 2018. As reported by the population projections, the percentage of the old people of the total population will be 10.2 % in 2023, 22.6 % in 2060 and 25.6 % in 2080. In other words, it is predicted that old population in Turkey will increase by 201 % during the years 2008-2040 (Samanci & Tekin, 2018). Based on life tables of 2015-2017, life expectancy at birth in Turkey is 78 years. Turkey is ranked 66 in countries by the elderly population ratio in 2018. As previously mentioned, Turkey is one of the most rapidly aging countries. Therefore, aging studies should deserve more priority in Turkey.

2.1. Aging Brain

Aging and senescence are the two common words used in gerontology that have similar meanings. Caeb Finch defined aging in his famous book as “any changes that occur during the passage of physical time, during which there need be not common mechanisms, such as the aging of collagen, the aging of diploid cells in culture or of erythrocytes in circulation, the aging of populations or societies, or the aging of genes and species during evolution” (Finch, 1994). On the other hand, senescence is described as age-related alterations observed in an organism which have negative effects on the functions and vitality.

Rather than the other organs of the body, the brain deserves a special treatment in terms of aging. Although there is parallelism between the changes derived from aging processes in brain and other organs, there are also some critical exceptions. Animal models of aging suggest that aging neurons exhibit approximately all features of aging observed in other tissues, including impressive plasticity with respect to environmental effects. Brain disorders generally are considered to be accompanied with aging, such as Alzheimer's disease (AD) and Parkinson's disease (PD). As an example, a gene that was discovered by Dr. Yankner and his colleagues is called repressor element 1-silencing transcription factor (REST) (Lu et al., 2014). This gene is switched on during fetal development and it is found that REST is reactivated in the brains of normal aging individuals (hippocampus and cortex) to repair the effects of stress. REST is in charge of turning off the genes which are responsible for Alzheimer's disease. Autopsies conducted on individuals whose cause of death was AD indicated that they have very little of REST protein, whereas individuals of the same age who died of different reasons have high level of REST. Rather than neuropathological aging, we will focus on healthy aging through this study.

MRI Perspective

Magnetic resonance imaging (MRI) is a popular medical imaging technique that used in determination of age-related structural and functional brain alterations. To construct images of the body strong magnetic fields and radio waves are used by MRI scanners. The wide usage of MR techniques in aging research can be ascribed to the need for obtaining information related with different properties of the brain tissue changes (e.g., brain metabolites like dopamine, choline, water content, myelin content) via numerous contrast mechanisms. The other characteristics of MRI which make it an ideal tool in aging research are being noninvasive and involving minimum risk.

There are some challenges in MRI related to the patients, especially old individuals. Claustrophobia stemming from the MRI atmosphere is a general issue observed in individuals from all age groups. Previously, it was reported that female

and middle-aged individuals (40–65-year-old) had significantly higher claustrophobia than the subjects older than 65 years of age (Dewey, Schink, & Dewey, 2007). Head motion artifacts (older adults move more than younger ones) (van Dijk, Sabuncu, & Buckner, 2012) and the difficulty of subject positioning in the scanner due to age-related spinal diseases comprise technical challenges of scanning of old individuals. Sedatives are commonly used to prevent motion-related artifacts so that image quality is improved. However, functional MRI (fMRI) data may be influenced by the sedatives. Moreover, elderly commonly use medical devices like neurostimulation devices (e.g., Parkinsonians), metal prostheses or dental implants which are ferromagnetic, increasing susceptibility artifacts for MR imaging.

This section focuses on structural changes in brain tissue accompanying healthy aging process in terms of MR studies.

2.1.1. Structural Changes

2.1.1.1. Brain Atrophy

There are several studies showing an age-related decrease in the size of the brain, which is defined as brain atrophy. This atrophy is composed of shrinkage of grey matter (GM) and white matter (WM) volumes and enlargement of the cerebrospinal fluid (CSF) spaces (Courchesne et al., 2000; Good et al., 2001.; Lemaître et al., 2005; C. D. Smith, Chebrolu, Wekstein, Schmitt, & Markesbery, 2007; Walhovd et al., 2005). These reports are supported with postmortem studies indicating that these age-related macroscopic alterations are attributable to histological changes which are more probably related to losses in the neuropil associated with reduction of dendrites and synapses, and loss of nerve fibers, rather than being related to direct losses of neurons (Pakkenberg et al., 2003; Peters, Morrison, Rosene, & Hyman, 1998). Also, there are studies investigating age effects in terms of regions of interest (ROI). According to these, vulnerability to aging across the whole brain varies regionally (Allen, Bruss, Brown, & Damasio, 2005; Good et al., n.d.; N Raz et al., 1997; Naftali Raz et al., 2004; Naftali Raz & Rodrigue, 2006; C. D. Smith et al., 2007; Tisserand et al., 2002;

Walhovd et al., 2011). For instance, lateral prefrontal cortex has been shown to be one of the most affected areas with advancing age (Abe et al., 2008; Allen et al., 2005; N Raz et al., 1997; Tisserand & Jolles, 2003; Tisserand et al., 2002). The hippocampus and the medial temporal lobe are among the regions that are also commonly implicated in healthy aging (Bigler, Andersob, & Blatter, 2002; Du et al., 2006; Walhovd et al., 2005). Cerebral cortical thinning starts in middle age, and spread out to several cortical regions such as association and primary cortices (Salat et al., 2004). Interestingly, age-related alterations of brain volumes among Alzheimer's disease (AD) or normal controls do not exhibit a sex influence (Salat et al., 2009). A meta-analysis including longitudinal and cross-sectional neuroimaging studies indicated (Fjell et al., 2010) that there is a correlation between brain atrophy and age even in subjects who are younger than 60, suggesting a linear trajectory of brain atrophy over time. This study includes healthy aged individuals and AD patients from the AD Neuroimaging Initiative (ADNI). They excluded the participants with cognitive decline (based on a two-year follow-up cognitive data of elderly individuals and ADNI group) and the significant brain atrophy in all ROIs was still persistent. These studies answer a debated scientific question that address whether brain atrophy indicates neurodegeneration (as in AD) or simply result from a healthy aging process. It is probable that brain atrophy occurs as a consequence of normal aging and an underlying pathologic neurodegeneration is not a necessity. There are different estimations of yearly atrophy rates reported in longitudinal (higher) and cross-sectional studies (Du et al., 2006; Naftali Raz et al., 2005a; Scahill et al., 2003). A decrease of annual whole brain volume reported in longitudinal studies varies between 0.2-0.5% (Ezekiel et al., 2004; Scahill et al., 2003).

2.1.1.2. Iron Accumulation

MRI is a widely used tool suitable for the assessment of regional iron concentration in the brain. Iron is a paramagnetic material with high magnetic susceptibility. There are various MRI techniques which are capable of detecting iron deposition in brain for example, susceptibility-weighted imaging (SWI), field-dependent relaxation rate

(FDRI) (Bartzokis et al., 1997), gradient recalled echo (GRE) and magnetic field correlation (MFC) (Adisetiyo et al., 2012).

In 1958, the Hallgren and Sourander reported that nonheme iron concentrations (generally in the form of ferritin) in brain structures were significantly higher in older individuals than in younger counterparts (Hallgren & Sourander, 1958). This has been interpreted as a biomarker of changes in neuroanatomical structures and cognitive declines accompanying normal aging process. Increased levels of iron cause oxidative stress in cell hence, age-dependent structural declines and neurodegenerative diseases might be attributed to iron accumulation-related cell degradation (Daugherty & Raz, 2013). According to postmortem studies, increases in iron content is regionally specific to subcortical area with in a prominent structure - basal ganglia (which is known to be also related to dopamine). In line with this, a meta-analysis showed that there is a robust relationship between increasing age and higher iron content in substantia nigra and striatum (i.e. caudate nucleus, putamen, nucleus accumbens and olfactory tubercle) (Daugherty & Raz, 2013). Iron accumulation rates change according to the brain structures and age period. Generally, iron concentrations in the striatum and brainstem are higher in older participants than in younger ones, however lower iron concentrations are observed in cortical WM and thalamus in elderly (Bilgic, Pfefferbaum, Rohlfing, Sullivan, & Adalsteinsson, 2012). Hippocampus is another region reported in iron related changes during aging. Higher iron concentrations in hippocampus and smaller hippocampal volume were related with lower memory scores (Rodrigue, Daugherty, Haacke, & Raz, 2013). The age-related iron-memory relationship was also demonstrated in a recent study which states that iron accumulation in ventral striatum is linked to the memory impairments and demyelination (Steiger, Weiskopf, & Bunzeck, 2016). Apart from studies mentioned above, different imaging techniques such as relaxometry are utilized to asses brain iron concentration changes with age (Aquino et al., 2009; Cherubini, Péran, Caltagirone, Sabatini, & Spalletta, 2009; Ghadery et al., 2015).

2.1.1.3. Quantitative MRI (qMRI or Relaxometry)

Generally, imaging scientists and clinicians are familiar with T_1 or T_2 weighted images while they interpret the tissue contrast and related information. The tissue contrast in conventional structural imaging is based on the sensitivity of the MRI signal based on relaxation times of underlying tissue. Adjustment of pulse sequence and control of acquisition parameters (e.g. inversion time, echo time, flip angle, etc.) increase the signal sensitivity to tissue variability. The major contrast parameters investigated are the longitudinal relaxation time (T_1), the transverse relaxation time (T_2) and the proton density of tissue water (PD). Although the acquired signal may be T_1 , T_2 or PD weighted, its contrast still depends on a combination of T_1 , T_2 , T_2^* and PD, as well as external influences. These influencing factors are composed of other acquisition parameters, signal amplifier gains etc. The nonlinear mixture of signal sources combines with mostly unpredictable hardware corruption and makes the interpretation of the MRI signal even more challenging. Moreover, this complicated combination averts comparison of the intensity values across individuals or imaging centers (Deoni, 2010).

If the above-mentioned independent sources are separated through direct calculation of the relaxation times and proton density via qMRI, imaging data may be interpreted in a simpler way. The creation of T_1 , T_2 or PD ‘maps’ can aid better characterization of the brain tissue, improved tissue contrast and superior segmentation especially through aging process, as we have showed in our previous work (Aktaş Dinçer & Gökçay, 2018). Although standard structural MR imaging techniques enlighten age-dependent macroscopic alterations, underlying microanatomical changes and its relation to healthy and pathological aging process remain poorly understood. qMRI unveils such variation of physical properties of tissues (i.e. water content and metabolite concentrations) through life in a better way. T_1 and T_2 especially depend on local tissue density (such as water content), macromolecule, the concentration of paramagnetic particles (e.g. iron), lipid and protein composition. Region specific degrees of myelination and MRI contrast were reported to be highly correlated with

the the histological data (Fatterpekar et al., 2002; Fukunaga et al., 2010; Geyer, Weiss, Reimann, Lohmann, & Turner, 2011). Previously, it is reported that the contribution of the myelin to the spin lattice relaxation rate, R_1^1 , is prominent (Rooney et al., 2007a). Furthermore, it is worthy to revisit the age-related changes of iron concentration and brain atrophy with the qMRI point of view. It is demonstrated that the main driver of the age-related GM volume loss in subcortical area is the tissue property (e.g. iron) changes rather than atrophy (Lorio et al., 2014). Higher iron concentration in deep brain nuclei reduces the longitudinal relaxation time (T_1) (Patenaude, Smith, Kennedy, & Jenkinson, 2011). Recently, it is reported that there is a correlation between the higher iron concentrations in basal ganglia - indicating higher R_2^{*2} and age-related cognitive impairment regardless of accompanying brain abnormalities (Ghadery et al., 2015).

Thus, estimations of the MRI parameters are important biomarkers of brain tissue microstructure related to aging, disease, neuroplasticity and pathology (Bodgan Draganski et al., 2016; Geyer et al., 2011; Khalil et al., 2015; Louapre et al., 2015). Beyond the properties explained above, qMRI opens new perspectives for brain imaging by providing advanced information for image registration, segmentation, myeloarchitectonic studies and intracortical surface extraction (Bazin et al., 2014; Cohen-Adad, 2014; Dick et al., 2012; J. D. Lewis, Evans, & Tohka, 2018; Lutti, Dick, Sereno, & Weiskopf, 2014a, 2014b; Stikov, Campbell, et al., 2015; Tardif, Collins, & Pike, 2009).

In this study, we will focus on the T_1 relaxation time changes observed during healthy aging.

¹ $R_1=1/T_1$
² $R_2^*=1/T_2^*$

Deeper View into Aging Effects on T₁

Cross-sectional Studies

Aging effects on T₁ values in several GM and WM regions of individuals were investigated in previous cross-sectional studies. Comparison of the results among existing literature is complicated because of the differences in qMRI methodology (multispectral or single parameter), scope of the qMRI analysis (ROI or global) and age ranges. T₁ measured in cortical GM in late life periods was demonstrated to decrease due to aging process (Cho, Jones, Reddick, Ogg, & Grant Steen, 1997; Saito, Sakai, Ozonoff, & Jara, 2009; Steen, Ogg, Reddick, & Kingsley, 1997; Suzuki, Sakai, & Jara, 2006). Whereas, in an early study it was stated that T₁ also decreases through adolescence and reaches to the minimum value in 4th to 6th decade of life, then T₁ relaxation time begins to increase (Cho et al., 1997). A consistent increase of T₁ in WM is shown in older subjects (Breger et al., 2014; Cho et al., 1997; Steen et al., 1997; Wahlund et al., 1990). Basal ganglia is one of the key regions that has been reported to have higher T₁ with increasing age (Cho et al., 1997; Steen et al., 1997). T₁ is decreased in the first half of life in thalamus, substantia nigra and globus pallidus and then shows a reversed pattern in such a way that it increases during the latter half (Badve et al., 2015; Jara, Sakai, Mankal, Irving, & Norbash, 2006). Callaghan and colleagues reported negative correlations between R₁³ and age in bilateral optic radiation and genu of the corpus callosum (Callaghan et al., 2014). In a recent study, age dependent T₁ alterations in deep GM area were investigated in 70 healthy subjects (Okubo et al., 2017). Magnetization-prepared 2 rapid acquisition gradient echoes (MP2RAGE) method is used for T₁ mapping. The authors reported a significant increase T₁ in thalamus and WM whereas a decrease in amygdala, nucleus accumbens and the ventral-inferior putamen is observed.

³ R₁=1/T₁

Longitudinal Studies

Despite the abundance of cross-sectional studies on age-related T_1 changes, only a few longitudinal designs were conducted. Recently, T_1 in cortical and subcortical area were investigated in a 7 year period longitudinal study to assess the normal aging patterns especially on 5th to 8th decade of life (Gracien et al., 2017). They reported age-driven significant T_1 decrease of GM in the cortex. Contrary to previous studies reporting a significant increase in T_1 in WM analyses (Andersen, 1997; Cho et al., 1997; Steen et al., 1997), Gracien et. al did not observe such an increase.

Although there are conflicting outcomes in the studies investigating age-related T_1 variations in the brain, it has to be kept in mind that T_1 relaxation time is a parameter affected by:

- water content (positive linear relationship) (Fatouros, Marmarou, Kraft, Inao, & Schwarz, 1991; Neeb, Zilles, & Shah, 2006),
- iron concentration (negatively correlated) (Gelman, Ewing, Gorell, Spickler, & Solomon, 2001),
- myelination degree of the underlying tissue (negative relationship) (Lutti et al., 2014a).

If the predominant factor in the aging brain is demyelination, then prolongation of T_1 is observed (Bock, Kocharyan, Liu, & Silva, 2009; Dinse et al., 2015). Thus, the direction of the change in T_1 due to healthy aging depends on the weights of the contribution of the above-mentioned microstructural properties. Additional to individual aging patterns of differences among subjects, the inconsistencies between the studies in the literature may be explained by several other factors such as the differences in preferred T_1 mapping method, ages of the subjects as well as sample size.

2.1.2. Cognitive Changes

2.1.2.1. Memory

Memory is the basis of higher cognitive functions (Loosli, Rahm, Unterrainer, Weiller, & Kaller, 2014; Süß, Oberauer, Wittmann, Wilhelm, & Schulze, 2002) that changes over the course of life. These changes might be beneficial and represent increased knowledge and experiences. On the other hand, other alterations in memory may indicate a destructive cognitive decline. Neuroimaging studies showed that age-related functional and structural declines in hippocampus are prominent (Larry R. Squire, 1992). Age-related memory decline is frequently reported in declarative memory, a type of long-term memory, which is dependent to hippocampal complex (Eichenbaum, 2000; L.R. Squire & Zola, 1996; Larry R. Squire, 1992, 2004; Tulving & Markowitsch, 1998).

Memory decline accompanying healthy aging is introduced as an age-associated memory impairment that is clearly distinguishable from the memory impairment in dementia. In fact, most of the individuals in older ages do not suffer from dementia, rather they have the “normal” memory decline (Plassman et al., 2007). Although the underlying biological mechanisms of such decline have not been understood yet, some risk factors of the pathological memory impairment have been described. Instead of an individual risk factor causing healthy aging related memory decline, it seems to be a complex combination of several risk factors are hereditary as well as, hypertension, stroke and traumatic brain injury related (Patterson et al., 2008; Scalco & van Reekum, 2006).

Additionally, age-related differences in working memory performances have been consistently reported (Basak & Zelinski, 2013; F. I. m. Craik, 1994; Loaiza & Oberauer, 2016), and this is supported by neuroimaging studies (Naftali Raz et al., 2005b; Reuter-Lorenz & Park, 2010; Rypma & D’Esposito, 2000; West, 1996).

There are different possibilities in which age-related memory declines may not indicate deficits in memory per se. There is a tendency to ignore the well-established

aging effects on sensory processes in designing and interpretation of cognitive studies (Schneider & Pichora-Fuller, 2000). The effortfulness theory (McCoy et al., 2005) provides evidence that some of the memory deficits observed in elderly may be caused by the encoding limitations which comes from compensation strategies – allocation of cognitive resources for sensory problems.

2.1.2.2. Processing Speed

The state of the art perspective on cognitive changes in aging processes is established on a framework which states that the processing speed in the nervous system is the base mechanism related to age-dependent alterations in behavior (Lester, Vatterott, & Vecera, 2017). Information processing speed in the central nervous system (CNS) lies in the heart of the cognitive functioning. There are ample number of studies showing that processing speed decreases in aging (Albinet, Boucard, Bouquet, & Audiffren, 2012; Cona, Arcara, Amodio, Schiff, & Bisiacchi, 2013; Manard, Carabin, Jaspar, & Collette, 2014; Salthouse, 2000). The response times of older adults are generally longer, independent of used task, since all cognitive phases are accomplished slower (Salthouse, 1996).

Neuroimaging data support the age-related changes in processing speed. WM integrity is decreased and also cerebral volume is reduced in aged brain (Rabbitt et al., 2007). Soderlund et. al reported that age-related periventricular WM hypersensitivities were associated with decreased motor speed (Söderlund, Nyberg, Adolfsson, Nilsson, & Launer, 2003). Among all processing speed measures (decision speed, psychomotor speed etc.), Salthouse found that contribution of the perceptual speed to the relationship between aging and cognition is higher than the motor speed (Salthouse, 1994). Furthermore, there are significant correlations between Diffusion Tensor Imaging (DTI) measures and performances of old adults on processing speed and executive functioning tasks (O’Sullivan et al., 2001; Persson et al., 2006; Stebbins, Poldrack, 2001).

2.1.2.3. Attention

Neuropsychological tests have been widely used to assess age-related alterations (Christensen, 2001) in attention, executive functioning and memory (Drag & Bieliauskas, 2010). The two crucial components of the attention are inhibition and selective attention. Healthy aging causes changes in inhibition, altering the ability to focus on task related information and to inhibit the information irrelevant to the task, defined as selective attention (Pergher et al., 2019). Although age-related changes of inhibition and selective attention exist (Barr & Giambra, 1990; Brink & McDowd, 1999; Mapstone, Dickerson, & Duffy, 2008; McDowd & Craik, 1988), sustained attention relatively remains unaffected (Berardi, Parasuraman, & Haxby, 2001; Filley & Cullum, 1994).

Additional to memory decline derived from hippocampus, it is demonstrated that prefrontal cortex-dependent attention processes are also exposed to aging (Hedden et al., 2012; Prakash et al., 2009). The decreases in inhibitory control have been shown to be associated with changes in prefrontal functioning (Chao & Knight, 1997; West, 1996).

Divided attention is another source of difficulty for elderly when simultaneous attendance to multiple sources and processing information from these sources are required. Although multi-tasking deteriorates the cognitive functioning of even the young adults, the older adults are more susceptible to be negatively affected by divided attention. It is consistently shown that older individuals' performances on tasks such as recognition memory, short-term memory under divided attention decreased (N. D. Anderson, Craik, & Naveh-Benjamin, 1998; Castel & Craik, 2003; Naveh-Benjamin, Guez, & Marom, 2003; Verhaeghen, Steitz, Sliwinski, & Cerella, 2003). Analogous to divided attention, another age-related deficit is task-switching which is the ability to fast shifting among different tasks (Kramer, Hahn, & Gopher, 2003; Kray, Li, & Lindenberger, 2002). Dorsolateral and medial prefrontal cortex and frontoparietal

white matter tracts activity has been associated with task switching in previous fMRI studies (DiGirolamo et al., 2001; Gold, Powell, Xuan, Jicha, & Smith, 2010).

2.1.2.4. Time Perception

Before the presentation of the age-related changes in time perception, models attempting to explain temporal processing will be summarized.

The operationalization of temporal perception poses certain difficulties because the concept of time is a difficult concept to grasp. Although it is easy to define time as a measure of the spacing between two events -as Aristotle asserted that time does not exist without events-, what happens to this definition when nothing happens? Time seems to flow well and truly in the absence of events, making its definition all the more complicated. One way of circumventing the ambiguities that the nature of time poses, when developing a definition, is based on the analogy of the hourglass with the notion of accumulation, which has inspired the contemporary models of perception. time.

Due to its high level of abstraction, the difficulties of defining time also apply when it comes to defining the perception of time. Grondin (2001) reviews the main issues relating to time and in particular how to perceive it. It is first necessary to distinguish, as Wilhelm Wundt did early, the sensation of being lost. According to him, sensation comes down to the direct sensory translation of the external world (quantifiable in terms of quality and intensity), whereas perception is the complex organization of sensory information. This complex organization allows the emergence of spatial perception, but also of temporal perception. Psychophysical studies have since demonstrated that temporal perception is an emergent feature of a percept (a mental representation of an object or a physical reality through perceptions) and that it is highly contextual. The perception of time does not have its own receivers, unlike perceptions from visual, auditory and tactile systems, which complicates the study of time even more.

Models of Perception of Time

On cognitive or neurobiological bases, several models of the perception of time have been proposed to try to understand the mechanisms associated with this phenomenon. These models provide explanations of a cognitive or neurobiological nature. In contrast, neurobiological models most often incorporate cognitive models and attempt to identify the biological corollaries of cognitive components. Some of the most influential and popular models in the literature are discussed below. It is appropriate to mention that these models are not necessarily mutually exclusive and rather attempt to account for different phenomena such as the proportionality of variability according to the magnitude of temporal judgments for scalar models or the effect of cognition on temporal perception for non-scalar models.

i. Cognitive Models

In order to better understand the processes involved in the perception of time in humans, different models have emerged. Cognitive models of time perception use cognitive components such as memory and attention to explain the mechanisms of temporal perception. It is possible to group these models into two categories: models focusing on the scalar component (so-called “scalar models”, like the model of the internal clock) and models focusing on non-scalar components (so-called “non-scalar models”, such as cognitive models and dynamic expectations).

The scalar models discussed below are more precisely those of Gibbon and Church (1984), Treisman (1963) and Treisman, Faulkner, Naish and Brogan (1990). The non-scalar models discussed here are the models of Ornstein (1969), Thomas and Weaver (1975), Zakay and Block (1997) and Barnes and Jones (2000).

The Scalar Models of the Perception of Time

The scalar expectancy theory of time is the theory most frequently cited in the perception of time in the 1990s (Grondin, 2001). The base of this theory is the idea that the variance of temporal judgments comes from three different levels of process (clock, memory, and decision-making processes) and that it has multiplicative

properties to fit with the scale (Grondin, 2001). Although Creelman (1962) was one of the first to propose a clock process using a transmitter and a counter to perceive time, the fact remains that the scalar theory of time has more. Thus, this theory directly follows the internal clock model of Gibbon and Church (1984), and later, the internal clock model with calibrated time transmitter of Treisman et al. (1990).

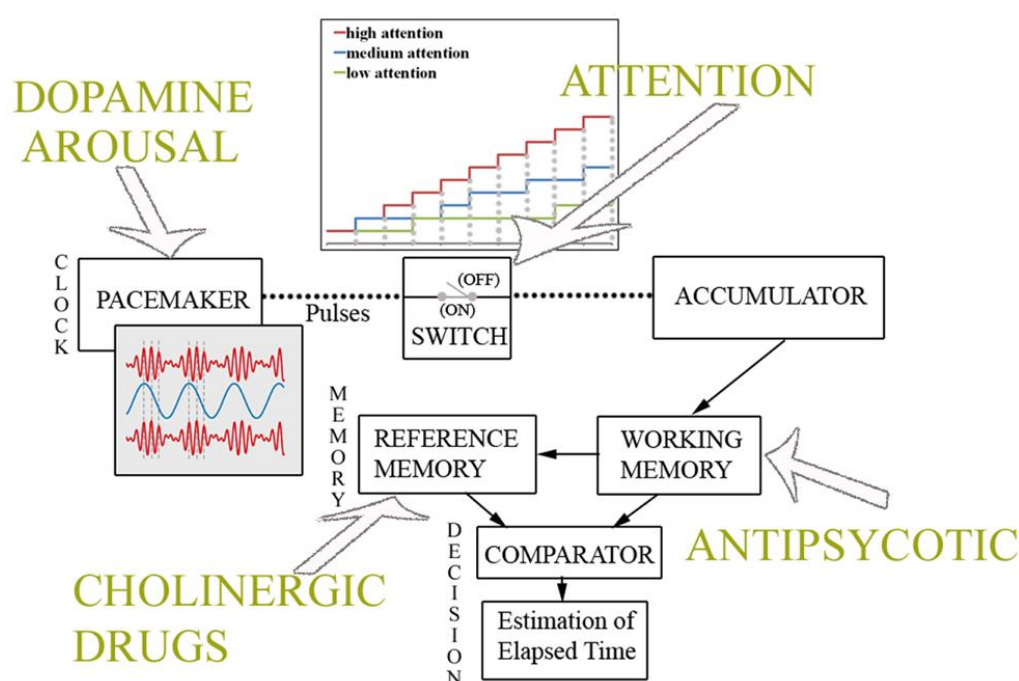


Figure 2.1. Cognitive model of time perception. Taken from Piras, F., Piras, F., Ciullo, V., Danese, E., Caltagirone, C., & Spalletta, G. (2014). Time dysperception perspective for acquired brain injury. *Frontiers in neurology*, 4, 217. Permission is not required for the reuse of this image.

The “information processing” version of the scalar theory of time: the internal clock model of Gibbon and Church (1984). Like the scalar theory of time, the internal clock model of Gibbon and Church (1984) is the most quoted model in the literature. According to this model, the internal clock is composed of a transmitter that emits pulses, a switch that modulates the number of pulses according to the attention

given to time (Grondin & Rammsayer, 2003), and an accumulator. The more attention is paid to time, the more the switch lets impulses go by and the longer the time. This is why, on the contrary, time seems shorter if less attention is given to time. The pulses then accumulate in the accumulator in order to be transferred back into the working memory (memory responsible for retaining the comparator) and to be compared with a standard in reference memory (memory responsible for retaining the standard). The decision-making processes then intervene to make a temporal judgment. A faster clock (which emits more pulses) will cause a perceived time longer than a slower clock. Therefore, this model is most often used to explain the perceptual processes of time.

The internal clock model of Treisman et al. (1990) with calibrated time transmitter. Treisman (1963) proposes the first three-level internal clock model, which he will later reconsider by specifying that the transmitter's timing can be calibrated to the sensory processing (Treisman, 1963). Thus, Treisman et al. (1990) present a model consisting primarily of a time emitter that emits pulses at a constant rate. Conversely, unlike the Gibbon and Church model (1984) which does not address this aspect, Treisman et al. (1990) argues that the transmitter's rhythm can take several frequencies after having been modulated by a calibration unit in order to be consistent with the sensory afference. In the absence of sensory afferences likely to interfere with the transmitter, it emits pulses at a rate peculiar to itself and this rhythm corresponds to a frequency of oscillation which is comparable to a natural frequency. The pulses are emitted by the transmitter at a regular rate, before being processed by the calibration unit which adjusts the rhythm to the sensory afferences resulting in the final output frequency, before sending them to the counter. A storage unit, used as a reference, makes it possible to compare the pulses counted by the counter to those in the storage unit and thus makes it possible to carry out a temporal judgment.

Non-scalar models of the perception of time

Ornstein's model (1969) is one of the first cognitive models. It does not use any clock or timing process and relies only on the use of cognitive resources to measure time.

According to this model, the perception of time would be a derivative of the processing of non-temporal information and would be influenced by the number and complexity of this information in memory. The perceived duration of an event would be proportional to the space occupied in memory by this event and also by its complexity. For the same duration, the presentation of a well-organized event in memory (e.g., a word) would be perceived as shorter than a complex and poorly organized event (e.g., the presentation of a word). Although there is some empirical support for the model (Thomas & Brown, 1974), according to Block and Zakay (1996), it would be the number of changes (or events) occurring during a given period that would have a greater influence on the perceived duration than the space occupied in memory. This model is now recognized to be more applicable to retrospective judgments (recall the duration of an event) than to prospective judgments (pay attention to the duration of an event), due to the memory component associated with the model (Hicks, Miller, & Kinsbourne, 1976).

The model of Thomas and Weaver (1975). In a context of limited cognitive resources, the model of Thomas and Weaver (1975) proposes the existence of two processors operating in parallel. A first processor would be assigned to the processing of non-temporal information and would thus deal with operations related to common cognitive processes. This model suggests the existence of a second processor, which would be dedicated solely to the processing of temporal information. The attention paid to time would influence the perception of time according to this model. In the event that more attention is given to time, the temporal processor would then receive more cognitive resources and the time elapsed would be more important. Conversely, in the case where attention is focused on non-temporal information, the temporal processor would receive fewer cognitive resources and the perceived duration would be less. Although it is an interesting concept, this model has received bitter criticism because of the difficulty of dissociating what is temporal information from non-temporal information. It becomes difficult to discern that the brain would be able to

automatically dissociate temporal information from non-temporal information, since this information is generally nested.

The model of Zakay and Block (1997). In an avowed goal of integrating scalar and non-scalar cognitive models of time perception and giving an important place to attention, Zakay and Block (1997) propose the model of the “attentional gate”. This model succeeds Zakay’s “resource allocation” model (1996). Although classified in the non-scalar models, this model integrates several scalar components, but has the particularity of emphasizing the attentional component. The attentional gate model is somewhat of a hybrid between Treisman’s (1990) model and that of Thomas and Weaver (1975). Its main characteristic is to add a “gate” to classical scalar models (like that of Gibbon & Church, 1984 and Treisman, 1990) between the transmitter and the switch. When the door opens, time information (especially pulses from the transmitter) can be transferred through the switch to a cognitive counter (i.e., the accumulator). The more time there is attention (or the longer the gate is open wide), the longer the perceived duration will be important. According to this model, the switch transmits the temporal information to the accumulator, upon receipt of the start signal, which would be associated with the “temporal significance” of the stimulus. When a stimulus indicating the beginning of a relevant time interval is perceived, the switch opens, the number of pulses in the accumulator is reset and it can begin to accumulate pulsations. After the second signal indicating the end of the interval in question is received, the accumulated pulses are transferred to working memory for comparison with the reference memory.

Like the Treisman model (1990), the number of pulses transmitted to the accumulator would depend on the frequency of the clock (which would be influenced by wakefulness, circadian rhythms etc.). This specificity of the model has the advantage of enabling it to take into account observations made with retrospective judgments. In retrospective judgments, there is less attention to time compared to prospective

judgments, which results in the “gate” being opened more closely and therefore the magnitude and accuracy of judgments are diminished. Unlike the previous scalar models, this model has the characteristic of making attention a pivot of the perception of time, suggesting that it would be the attention to controlled time and not an automatic attentional process that would influence the perception of time. Attention to time could then be divided between temporal and nontemporal information voluntarily, in agreement with the experimental data on this subject (Macar, Grondin, & Casini, 1994).

The model of Barnes and Jones (2000). The model of dynamic expectations (initially formulated by Jones & Boltz, 1989) is not based on a clock mechanism, nor on a mechanism of accumulation or counting of pulsations. This model advances rather than the indices found in the environment and the synchronization of events would be sufficient to allow the emergence of the perception of time. The structure, coherence and regularity of events in the environment (with a definite beginning and end) allow temporal predictions that influence expectations towards the future.

The original model of Jones & Boltz (1989) was refined by Barnes and Jones (2000), including a series of experiments that put it to the test and specify it. Rather than proposing a conventional transmitter (or oscillator) as in the previously described models, this model defines the existence of a non-linear attentional oscillator with a limit cycle. The oscillator would emit attentional energy pulses, which synchronize with the phase and frequency of physical stimuli. This new model of dynamic expectations therefore provides for precise temporal judgments in situations where the stimulus is predictable (the prediction is influenced by previous experience of the target duration) and less accurate judgments when the target stimulus appears in a phased manner with the attentional oscillator.

ii. Neurobiological models

Meck (1996) summarizes the neuronal basis of the internal clock and advances a scalar neuropharmacological model of time perception. Referring to numerous pharmacological evidences, but particularly to the fact that a neuroleptic such as haloperidol, a dopamine receptor antagonist, acts at the level of the internal clock (slowdown of the internal clock), this model is based on an internal clock probably modulated by dopaminergic system of the individual. The memory and attentional components also involved in temporal judgments would be modulated by acetylcholine (neurotransmitter known to be involved in cognition) of the frontal cortex (region associated with higher cognitive processes). The involvement of glutamate remains to be determined. In this model, the fronto-striatal loop has the function of linking the striatal clock process to the frontal cognitive processes involved in temporal judgments.

The most recent support for Meck's (1996) model is synthesized by Buhusi and Meck (2005) in a literature review on the neural bases of time perception. As Meck's (1996) model suggests, there would be a dissociation between a dopamine-mediated clock process and the memory and decision-making processes that would be modulated by acetylcholine. Buhusi and Meck (2005) present a model that summarizes very well the data supporting this hypothesis (Fig. 2.2). Fig. 2.2a shows that dopaminergic antagonists produce a deceleration of the subjective flow of time, which would take place at the level of the transmitter of the internal clock. In addition, Fig. 2.2c shows that the amplitude of this subjective deceleration is proportional to the dopamine D2 receptor affinity of the antagonists. A similar phenomenon of deceleration of the subjective flow of time is observed with the muscarinic cholinergic receptor antagonists of the frontal cortex. This phenomenon would be associated with the reference memory. Fig. 2.2f shows that a correlation is observed between the importance of the slowing down of the perceived duration and the activity of the cholinergic neurons of the frontal cortex. Buhusi and Meck (2005) point out that the results of studies with different dopaminergic antagonists are not always constant and

that they would influence not only the rhythm of the internal clock, but also the attentional processing of temporal information.

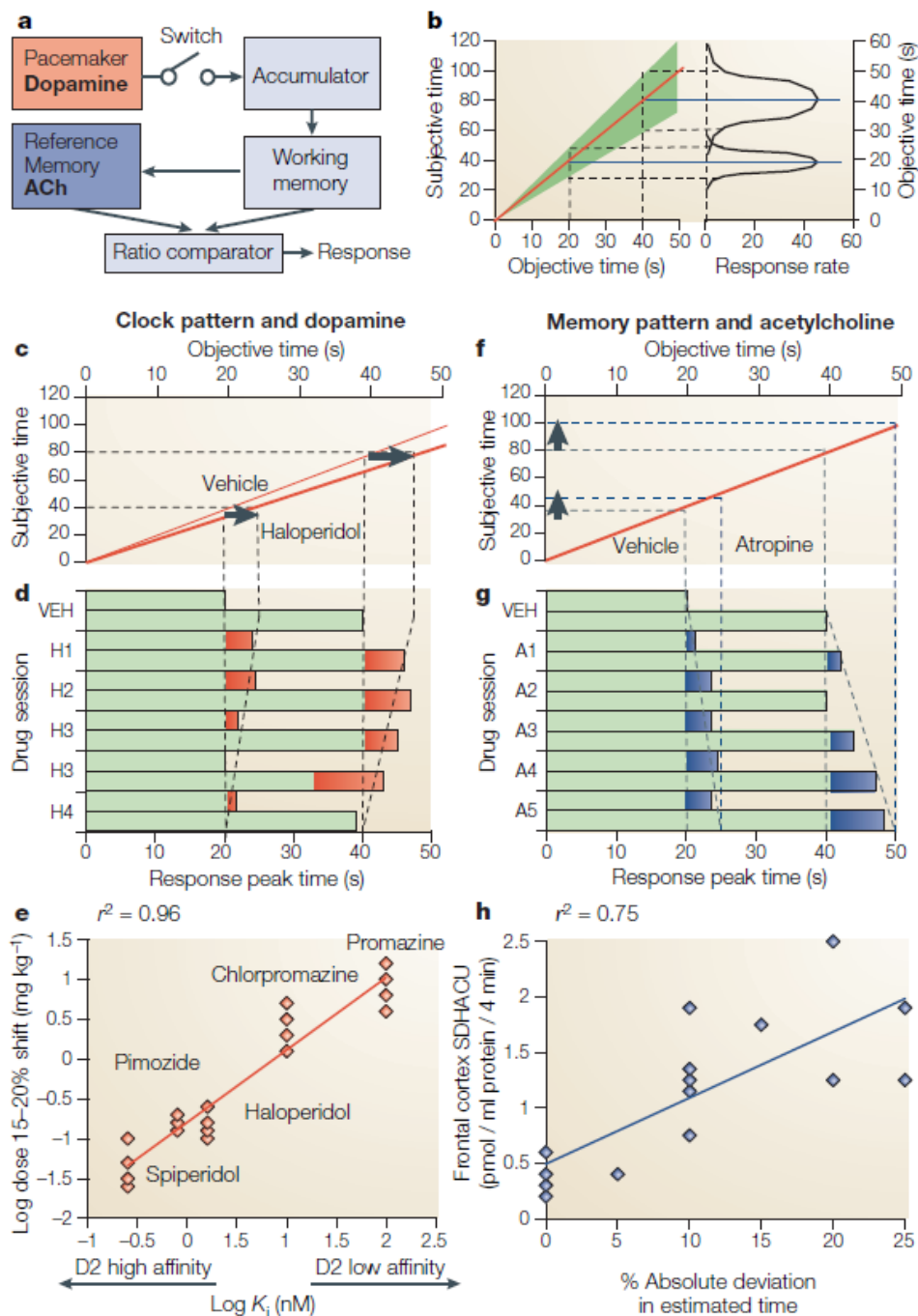


Figure 2.2. The pacemaker-accumulator model and dopaminergic and cholinergic synapses. Reprinted with the permission from Springer Nature Customer Service Centre GmbH: Nature, 'What makes us tick? Functional and neural mechanisms of interval timing' by Buhusi & Meck, Copyright © 2005.

A phenomenon of interest with regard to the effects of the different pharmacological agents on the perception of time is the dissociation between a temporary or lasting effect through the different sessions, according to the substances. Fig. 2.2d shows that through the different sessions (H1 to H4), the shift to the right (sign of temporal underestimates) of the psychometric function diminishes until it is resorbed with haloperidol. In doing so, even if haloperidol slows the rate of the internal clock, this effect would not be sustainable due to a “recalibration” during the encoding of durations. The durations, shortened by the effects of haloperidol, would be compared to a standard also shortened and would cancel the effect of the substance on the perception of time. The situation is different with cholinergic antagonists (Fig. 2.2g), which cause a lasting effect on temporal judgments.

Gibbon, Malapani, Dale and Gallistel’s model (1997). Gibbon et al.’s (1997) model focuses on thalamocerebellar interactions and focuses on the deleterious effects of cerebellar lesions on the perception of time. The lesions in the cerebellum would produce dysfunction of tonic neuronal functioning in the thalamus, which could result in disordered thalamic control. It has been observed that cerebellar lesions produce additional interferences in the thalamus, which would interfere with striathalamocortical loop communications. This plays a critical role in the encoding and comparison in memory of the time intervals. A dysregulation of the thalamic control would explain the deficits in the perception of time caused by the cerebellar lesions. This is explained according to Gibbon et al. (1997) not in terms of clock processes, but rather in terms of disturbances in encoding and in memory retrieval of temporal information, via a thalamocortical loop affected by cerebellar lesions. However, Gibbon et al. (1997) admit at this time that there are few studies to support their model and that animal injury studies would help support it. Recent studies confirm that cerebellar lesions in humans disturb the perception of time, but the exact significance of these disturbances remains controversial because of the known implications of the cerebellum in motor coordination.

The model of striatal beat frequency (SBF) by Matell and Meck (2000). In an attempt to integrate the most recent knowledge on the neurobiological mechanisms of temporal perception, Matell and Meck (2000) propose a model based largely on the striatum. Based on the properties of the dopaminergic system, striatal structures and striatal neurons, this model explains the neuronal functioning of the internal clock component of the Gibbon and Church model (1984). From pharmacological, lesional and brain imaging studies, basal ganglia are recognized as key structures in the perception of time (Matell & Meck, 2000; Matell, Meck, & Nicolelis, 2003a, 2003b; Meck, Church, Wenk, & Olton, 1987). The striatum has all the properties necessary to act as a “coincidence detector”. Receiving several thalamocortical afferents from the cortico-striato-thalamocortical loop (Fig. 1.3), each neuron of the striatum has from 10.000 to 30.000 dendritic spines. These spines are designed to receive each thalamocortical afference of multiple neurons from these regions. In the resting state, these neurons are rather silent and they only activate after a large number of related discharges, at a rate between 5 to 20 ms. An average neuron is more easily excitable, since it is activated with a rate of afferent discharges between 20 to 100 ms. In addition, these neurons are subject to long-term potentiation mechanisms (better known as LTP) and long-term depression (LTD). In combination with brain plasticity, memory and learning, these two mechanisms alter the strength of pre- and postsynaptic interactions by modulating the amount of neurotransmitters released presynaptically or the efficiency of postsynaptic receptors. This mechanism would then give the striatal spinal neurons the capacity to hypo- or hypersensitize themselves to afferents and thus fire only when a specific pattern of cortical afferents is presented. These neurons would act as a kind of recognition system and a detector of coincidences when previously reinforced cortical afferents are active at the same time.

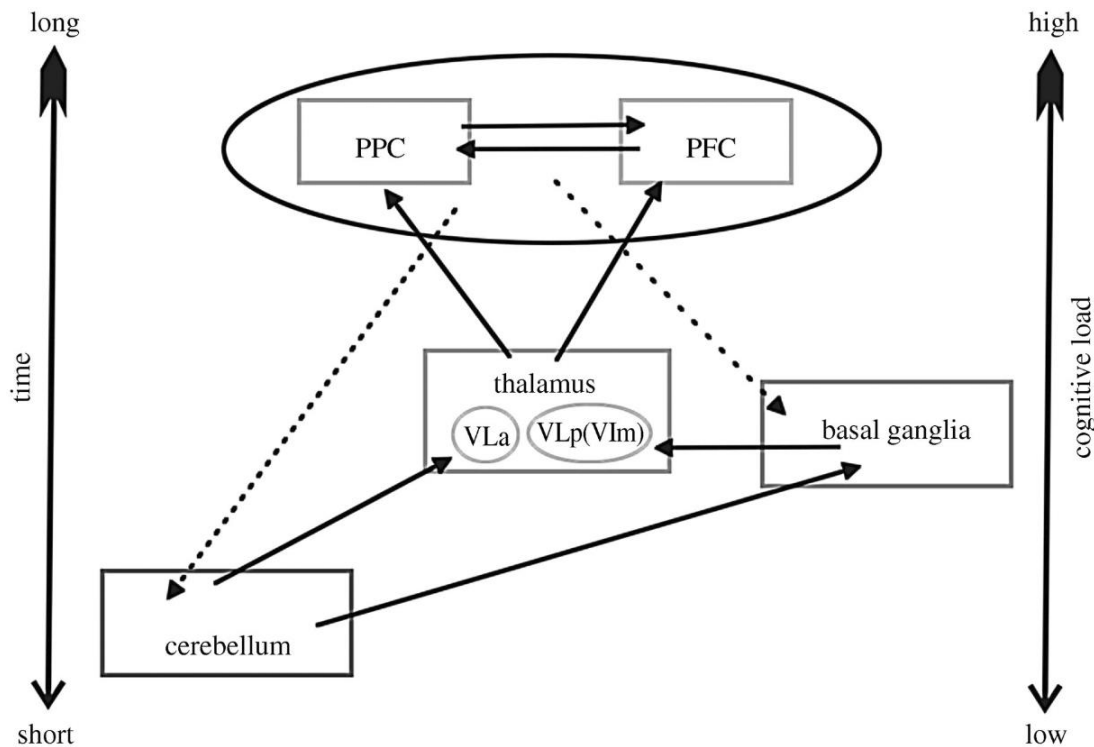


Figure 2.3. Cortico-striato-thalamocortical circuit. Schematic of the connections between the subcortical and cortical structures involved in time processing of time intervals with different durations and cognitive loads. The arrow in the left indicates length of time intervals and the arrow in the right indicates the difficulty of the task being performed. PPC, posterior parietal cortex; PFC, prefrontal cortex; VLa, anterior ventrolateral nucleus; VLp, posterior ventrolateral nucleus; VIm, intermediate ventral nucleus (taken from Koch, G., Oliveri, M., & Caltagirone, 2009).

The trigger of the cortical activity monitoring process by the striatum is related to the dopaminergic activity of the mesencephalic nucleus named substantia nigra pars compacta (SNpc). Upon the occurrence of a stimulus, the SNpc sends a dopaminergic discharge, which could be used to initiate the striatal timing mechanism by hyperpolarizing the striatal cells and synchronizing the cortical oscillators. The cortical neurons responsible for the representation of the new stimulus discharge in synchrony to the striatum, first in a phasic manner (simultaneously), then in a tonic manner (continuously). Stimulus activity and its rhythms vary as time goes by and this activity is consistently integrated with striatal neurons that associate particular cortical states with specific durations. It is the phasic release of dopamine by the SNpc at the appearance of a new stimulus that would allow the striatal neurons to learn which patterns of cortical activity are relevant and integrate them using the LTP or the LTD

(Bernardi et al., 1999; Wickens, Begg, & Arbutnott, 1996). The striatal neurons thus come to discharge when they recognize a pattern of neuronal activity associated with certain durations, which has been previously reinforced by a dopaminergic LTP. The striatal discharge is then mediated by the thalamus for behavioral response.

In their literature review, Buhusi and Meck (2005) provide additional support for the Matell and Meck model (2000). They report that Matell, Meck and Nicolelis (2003a) observed that the activity of stimulated striatal neurons in the rat increases before the moment of an anticipated reward and increases continuously before reaching its maximum at the target interval. These observations demonstrate the importance of striatal discharges, especially during temporal reproduction tasks. Given the variability, both in cortical oscillations and in the striatal discharge threshold, the model simulations result in a Gaussian behavioral response curve with scalar properties (Matell & Meck, 2004).

Age-Related Changes in Time Perception

“Time flies as we get older” is a well-known phenomenon. Although it is agreed that aging affects time judgements, the actual underlying mechanisms are still under debate (Turgeon, Lustig, & Meck, 2016). Previously, several studies were conducted to investigate the effects of both healthy and pathological aging on time perception (Balci, Meck, Moore, & Brunner, 2008; R. A. Block, Zakay, & Hancock, 1998; Sylvie Droit-Volet, 2016; Magalhães et al., 2018; Perbal, Droit-Volet, Isingrini, & Pouthas, 2003; Winkler et al., 2017). However, the conclusions of these studies are paradoxical: the reported age-related changes remain unclear about whether underlying cognitive factors are attributable solely on time perception. Reported effects of aging on performances in various timing tasks which range from milliseconds-to-minutes are generally slight or absent (Horváth, Czigler, Winkler, & Teder-Sälejärvi, 2007; T. H. Rammsayer, 1993). In most of the cases, age differences were attributed to age related differences in other cognitive functions such as memory, attention and processing speed (Bartholomew, Meck, & Cirulli, 2015; Desai, 2007; Krampe, Engbert, & Kliegl,

2002; Ulbrich, Churan, Fink, & Wittmann, 2007; Wittmann & Lehnhoff, 2005) or circadian rhythms (J. A. E. Anderson, Campbell, Amer, Grady, & Hasher, 2014; Lustig & Meck, 2001; MacDonald & Meck, 2005; Meck, 1991), rather than being attributable to temporal processing exclusively.

The first study that investigated aging in temporal tasks is in 1997 (J. H. Wearden, Wearden, & Rabbitt, 1997). They found that older participants (between ages 70 and 79 years) showed a decline in performance on a temporal generalization task, compared to a younger elderly group (between ages 60 and 69 years). However, they did not find any significant effect of aging in a temporal bisection task with short durations (<1 s). A meta-analysis conducted by Block et al. (1998) demonstrated that older adults overestimated and underproduced time compared to young adults. This suggests that older adults have a faster internal clock than young adults. These two age groups exhibit two main differences: first, older adults display a decreased accuracy in time judgments (their estimates have a greater difference with physical time than the estimates of younger adults). Second, older adults' time judgments are less precise; in other words, their temporal variability is greater, which indicates a lower sensitivity to time.

Generally, an information-processing framework is used to explain age-related differences in time perception (Allman, Yin, & Meck, 2014; Lustig, 2003; Meck, 1984; S. Vanneste, Pouthas, & Wearden, 2001; Sandrine Vanneste & Pouthas, 1999; Zakay & Block, 1997). In such a framework, an attentional gate and/or switch exists which allows the passage of time to the accumulator. The pulses passed to the working memory and a comparison of accumulated and standard values from reference memory is conducted (Gibbon, 1977; Treisman, 1963). If more pulses are accumulated, the judged time would be longer. There is adequate evidence that information processing is slowed down with aging (Craick, Fergus IM & Salthouse, Timothy, 2000; Salthouse, 1996). It is suggested that slowing down of the processing speed relates to a slower running internal clock. In a slower internal clock, durations are underestimated due to accumulation of fewer pulses. Furthermore, more noise is

produced by the slower clock during the timing and this is interpreted with more variable time judgements observed in elderly. From a neurological point of view, a gradual decrease of dopamine level in striatum has been related to the slowing down of the internal clock, which in turn causes the variability reported in older individuals (Meck, Penney, & Pouthas, 2008; Rubia, 2006; Rubia & Smith, 2004). Furthermore, healthy aging introduces a tendency of various brain areas to shrink which in turn affects the mediation of decreased temporal processing related to dopamine (Li, Lindenberger, & Bäckman, 2010). Nonetheless, there are not enough studies directly explaining this hypothesis. Clock recalibration, fast adaptation to the current speed of the internal clock, is proposed as a candidate explanation which may the related effects are masked (R. A. Block et al., 1998; J. H. Wearden, 2005).

On the other hand, the role of cognitive functions in the time perception of aging adults is not negligible, as reported in many studies (Lustig & Meck, 2001, 2011). The scientists in this branch emphasized that inaccuracy in the time judgments of elderly existed as a consequence of the reduction in cognitive functions such as working memory and attention. Various neurophysiological tests used for the assessment of individual cognitive capacities have pointed out that there are high correlations between cognitive abilities and temporal judgments.

When the results mentioned above are considered, it is worthy to say that the experimental task chosen to explore temporal judgements is important. Recently, Droit-Volet et al. (S. Droit-Volet, Wearden, & Zélanti, 2015) investigated age-related differences in different temporal tasks (bisection, generalization and reproduction) with short and long durations in the same individuals (children and adults) and measured associated cognitive capacities. In temporal bisection, participants categorize comparison durations as short or long. They reported that cognitive demands change as a function of the temporal task used, and that the bisection task was the least demanding task in terms of cognitive capacities. They were able to demonstrate that cognitive demands differ as a function of the preferred temporal task. No aging effects in temporal performance in time bisection tasks were observed in

various aging and developmental studies (Lustig & Meck, 2011; T. McCormack, Brown, Maylor, Darby, & Green, 1999; J. H. Wearden et al., 1997). The pioneering study of Wearden et al. (J. H. Wearden et al., 1997) reported no age-related differences in a temporal bisection task with short durations (<1 s), whereas a difference emerged in other tasks. Conversely, if the complexity of the task increased, requiring more cognitive demand, the aging effects became more prominent (Lustig & Meck, 2001, 2011). Likewise, Block et al. (R. A. Block et al., 1998) stated that age-related temporal differences may be emphasized by the task difficulty. Moreover, Lustig and Meck (Lustig & Meck, 2001) mentioned that a decline in attentional resources, which is a consequence of healthy aging, may explain some of these timing deficits.

In a recent study conducted by Lamotte et al, the time perceptions of young (mean age= 24.75, ranges between 21-27 years) and old participants (mean age= 79.16, ranges between 76-81 years) in a temporal bisection task with several different stimuli ranges from a few milliseconds to several seconds were analyzed and the cognitive capacities of each individual were assessed with various neuropsychological tests (M. Lamotte & Droit-Volet, 2017). The authors reported a lower sensitivity to time in older participants than in younger participants in all stimuli ranges; and this reduction in temporal sensitivity was explained by the deterioration of attention with aging. Although younger participants are flexible and can allocate attention to the characteristics of a task, the decline of cognitive functions such as executive attentional control may be one reason why older adults focus more on some other unrelated stimuli during the task (Lustig & Meck, 2001, 2011). According to some studies, more attention is necessary for processing of long (>2 s) durations (Jennifer T. Coull, Cheng, & Meck, 2011).

As indicated above, stimuli range is a crucial factor that affects the outcomes. Carrasco et al. (Carrasco, Bernal, & Redolat, 2001) analyzed the time estimations of young and old participants via temporal estimation tasks with a standard stimulus duration of 10 s and reported that the older participants produced shorter intervals than their younger counterparts; however, no differences were observed in the absolute error from the

target time and the standard deviation in their responses. These findings suggest that the underlying mechanisms may not have changed with aging, but the representations of the older individuals may differ from the young individuals in terms of content. For example, when older participants were supported by the appropriate feedback, they performed comparably to young individuals at shorter intervals (e.g., 1 s) (J. H. Wearden et al., 1997). However, in studies using long intervals in which daily activities had to be paused (such as Carrasco et al.'s study), older individuals exhibited a poorer performance compared to younger individuals.

Scaffolding Theory of Aging and Cognition (STAC)

The age-related structural changes (brain atrophy, decrease of myelination etc.) and cognitive changes such as declines in memory, processing speed have been previously reported. Although the deterioration of the above-mentioned functions exists, a significant increase of prefrontal cortex activation has been observed in functional imaging studies. Park & Reuter-Lorenz (2009) proposed STAC which was suggesting that aging brain adapted in such a way that the challenges derived from structural and cognitive deterioration are compensated by allocating more of the cognitive resources to the related task. The STAC model is summarized in Figure 2.4.

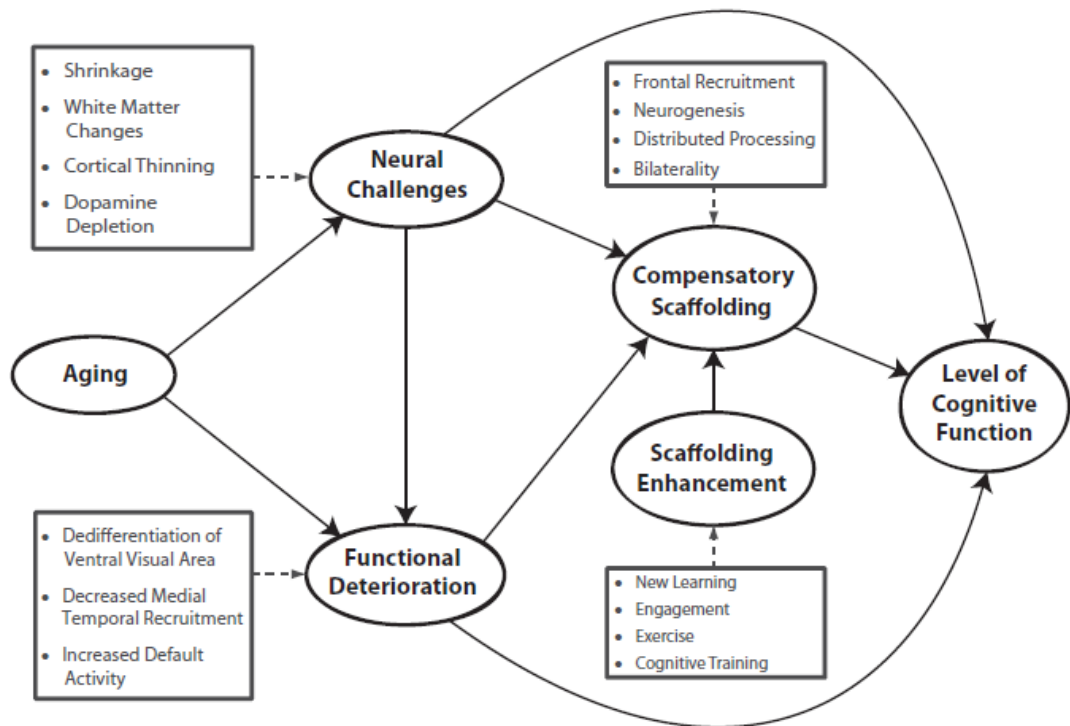


Figure 2.4. STAC conceptual model. Reprinted by the permission from Copyright Clearance Center Park, D. C., & Reuter-Lorenz, P. (2009). *The adaptive brain: aging and neurocognitive scaffolding*. *Annual Review of Psychology*, 60, 173–196.

2.2. Brain Areas & Time Perception

2.2.1. Localization of Time Perception

As early as in 1967, the importance of the cerebellum in timing processes is postulated (Braitenberg, 1967). According to lesion studies, Ivry and colleagues demonstrated for the first time that patients with cerebellar lesions displayed poor performance in both motor tapping and time-estimation tasks (Ivry* & Diener, 1991; R. B. Ivry, Keele, & Diener, 1988). Later on, this finding was supported by functional neuroimaging studies, in healthy subjects and patients with cerebellar lesions through the activation of both the medial and the lateral zones of the cerebellar cortex during

tasks requiring the precise representation of temporal information (Harrington et al., 2004; Kawashima et al., 2000).

Based on the lesion/injury studies and studies using patients with dopaminergic diseases such as Parkinson's and Huntington's disease, Buhusi and colleagues put forward two separate timing mechanisms working in parallel (Buhusi & Meck, 2005). This is supported by injury studies of Ravizza & Ivry (2001), in which patients with cerebral palsy and Parkinson's disease have difficulty with tasks requiring rapid alternation of attention and motor response. However, when the motor demand for the task is reduced, the cerebral-injured patients show a better performance than those with Parkinson's disease, suggesting that the cerebellar lesions cause deficits in the alternation of the motor response, while Parkinson's disease would be associated with difficulty in alternating attentional focus. These results and the fact that cerebral-injured patients show deficits in producing discontinuous movements and not continuous movements, indicate that the cerebellum may have a specific role in the timing of events. All these results suggest the existence of two distinct circuits when the motor and attentional aspects are separated. A first automatic system times discrete durations in milliseconds and makes better use of the cerebellum. A second timekeeping system in charge of continuous events, which requires attentional cognitive control based on the basal ganglia and related cortical structures. The fact that cerebellar lesions do not affect the temporal properties of temporal judgments in affected individuals, suggests for Buhusi and Meck (2005), that this structure is not essential for a proper perception of the long duration of time. In contrast, patients with Parkinson's disease, which is characterized by a decrease in dopamine of the nigrostriatal pathway, show affected scalar properties in temporal judgement when they are not on medication, whereas this is not the case when the medication is taken. The basal ganglia are therefore essential to the perception of time and the lesion studies also support this (for a review, see (Matell & Meck, 2004)).

A comprehensive review of the functional neuroimaging literature of time perception shows that at the subcortical level, there is a consensus regarding the role of basal

ganglia (especially the striatum) in early temporal processing. A role in the encoding of durations (Rao, Mayer, & Harrington, 2001) or a transmitter function of the internal clock (Jennifer T Coull, Vidal, Nazarian, & Macar, 2004) is most often attributed to this structure. There is a growing interest in recent years in the potential contribution of the basal ganglia (particularly striatum structures) to the perception of time while the cerebellum has long been the strongest candidate for the encoding of durations (Gibbon, Malapani, Dale, & Gallistel, 1997). The current models now attribute the role, which has been previously assigned to the cerebellum, to the basal ganglia (Buhusi & Meck, 2005; Matell & Meck, 2000; Meck & Benson, 2002). In comparison with the Gibbon and Church model (1984), several authors argue that the putamen and the caudate nucleus would be involved in the early representation of the temporal intervals (clock process), having an exclusive function in the fine discrimination or in the memory encoding of the time intervals. This is because when compared to a baseline condition at rest or a control task (often designed to control motor skills and attention), striatal activations are observed only for the temporal discrimination task (Livesey, Wall, & Smith, 2007; Marsault et al., 2003; Pouthas et al., 2005; Thomas Rammsayer et al., 2016). The fact that the putamen and the caudate nucleus are activated only during the encoding phase of the experiment suggests that structures are only involved in the encoding of durations (Rao et al., 2001). Moreover, it has been suggested that the role of the putamen (specifically left putamen) would not be limited to interval coding but would extend to decision-making processes.

Malapani et al (2002) reported that initial encoding of stimulus duration into memory in non-medicated Parkinson's disease (PD) patients led to overestimation of both short and long durations, suggesting that during duration encoding, basal ganglia may have a role in determining the speed of the internal clock. This finding is valuable because it is known that there is a dysfunction of dopaminergic neurons in basal ganglia of PD patients.

Functional neuroimaging studies showed that the areas most commonly activated by timing tasks are the putamen and caudate nucleus of the dorsal striatum, and its target

site within the basal ganglia, the globus pallidus (Jennifer T. Coull et al., 2011). Data from several well controlled fMRI studies are plotted in Figure 2.5 as a function of the perceptual or motor nature of the timing task. First, the figure shows that timing more often activates the putamen rather than the caudate nucleus of the dorsal striatum. Second, the clusters of activation suggest that motor timing tasks tend to activate more lateral regions of basal ganglia, predominantly in the putamen (dorsolateral striatum), whereas perceptual tasks tend to activate more medial regions, including the caudate and globus pallidus.

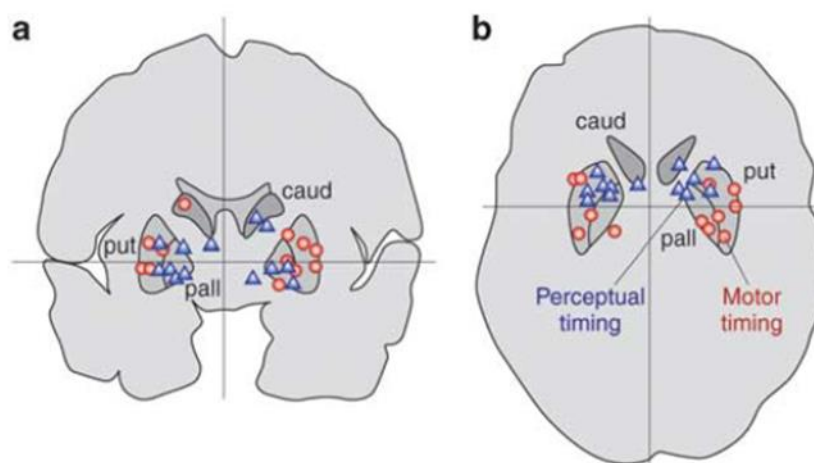


Figure 2.5. Most commonly activated subcortical areas in timing. Each point in this figure is a representative of timing-related activation cluster where amplitude peaks (blue triangles show perceptual timing; red circles show motor timing). Reprinted with the permission from Springer Nature and Copyright Clearance Center. Coull, Jennifer T., Cheng, R. K., & Meck, W. H. (2011). Neuroanatomical and neurochemical substrates of timing. *Neuropsychopharmacology*, 36(1), 3–25

Additionally, in a study conducted by Coull and colleagues a significant co-variation between basal ganglia activity and timing performance was reported (JT T. Coull & Nobre, 2008) which suggests that the depth of encoding of stimulus duration is mediated by the amplitude of activity in this area. Although there is a conflict in literature about the role of prefrontal cortex and its lateralization in human timing, there are numerous studies pointing out that the basal ganglia plays a critical role in

interval timing (Meck, 2003). In an fMRI study conducted by Hinton, Meck, & Macfall (1996), it is found that step one of the most reliably activated areas across all participants was the right putamen. Another fMRI study that is mentioned in (Meck, 2003) used a region-of-interest (ROI) analysis and two different durations to examine whether activation in the putamen could be reliably separated from that due to the motor response (unpublished data). They showed that the activation is stronger in the right than in the left putamen. Overall, timing is clearly separable from and anticipates those of the motor and sensory cortices.

Basal ganglia cooperates with a mixture of cortical structures that are anatomically discrete. This cooperation defines a functional network among corticostriatal regions for timing. Supplementary motor area (SMA) and prefrontal cortex are the two cortical regions most commonly reported to be activated during timing tasks, and these regions are included in prefrontal corticostriatal and motor loops defines in an early work (Alexander, DeLong, & Strick, 1986). Several previous studies indicated that despite the context-dependent activations in temporal tasks in several cortical regions, the role of SMA and basal ganglia have a key role in motor timing (Jantzen, Oullier, Marshall, Steinberg, & Kelso, 2007; Jantzen, Steinberg, & Kelso, 2005).

The thalamus is the intermediate structure of the striato-thalamocortical network, which would also be involved in the representation of time (Rao et al., 2001). On the other hand, while on one side there are advocates of the role of the cerebellum in the perception of time (Penelope A Lewis & Miall, 2003), who even attribute to it the potential role of an internal clock (A. Smith, Taylor, Lidzba, & Rubia, 2003), authors who question its involvement in the perception of time (Rao et al., 2001) argue that this structure could simply be involved in other cognitive functions. On other hand, at the cortical level, the frontal lobe (the prefrontal ventrolateral cortex and the dorsolateral prefrontal cortex are among the most frequently cited frontal regions) is most often associated with the perception of time with respect to attentional, memory, or decision processes, corresponding to the two higher levels of the Gibbon and Church model (1984). Only Lewis (2002), suggests that the dorsolateral prefrontal

cortex could act as a cortical oscillator, or even be the neuronal substrate of the internal clock. The dorsolateral prefrontal cortex is the cortical structure which received the most attention in relation to the perception of time in recent years. According to the different authors, its role in the perception of time could range from that of the internal representation of durations (Jennifer T Coull et al., 2004; Tregellas, Davalos, & Rojas, 2006) to that of the neural substrate of the transmitter of the internal clock in association with striatal afferents (Pouthas et al., 2005). Finally, the parietal lobe has most often been associated with attention given to time (Jennifer T Coull et al., 2004), which could correspond to the role of switch and accumulator (Harrington et al., 2004), but its role could also extend to decision-making processes. It is shown that patients with lesions to right prefrontal cortex similarly show timing deficits that are restricted to longer durations in many studies (Danckert et al., 2007; Kagerer, Wittmann, Szeglag, & Steinbchel, 2002). When the role of this brain region in planning complex cognitive behavior, personality expression, decision making, and moderating social behavior is taken into account this is an expected finding (Yang & Raine, 2009).

In a pioneering study, (Meck et al., 1987) demonstrated the critical role of hippocampus in timing and its relation with working memory. The most remarkable outcome stated in this study is the loss of the ability to sum signal durations across a break in the stimulus presentation observed in rats that have hippocampal damage. Another important role of the hippocampus is in trace conditioning and this shows the likely role of this structure as a short-term memory buffer for temporal intervals (Bangasser, 2006).

2.2.2. Neurotransmitters Taking Role in Time Perception

2.2.2.1. Dopamine

Increasing or decreasing dopamine levels in the brain result in different timing responses by speeding up or slowing down the subjects (Balci, 2014; Cevik, 2003; Maricq & Church, 1983; Maricq, Roberts, & Church, 1981; Matell, Bateson, & Meck, 2006; Meck, 1983, 1996). Aforementioned studies showed that if the dopamine levels

acutely increased (e.g. by injection of methamphetamine) in animals, that are trained on some timing tasks, the response given by the animal is interpreted as if time passed faster for them. Similarly, when a drug that decreases dopamine levels is injected, the opposite effect is observed (Drew, Fairhurst, Malapani, Horvitz, & Balsam, 2003; Meck, 1983, 1986). These outcomes support the dopamine clock hypothesis which states that the speed of the hypothetical internal clock is determined by the dopamine levels.

Different effects of dopamine modulation on timings is demonstrated on human data as well (Drew et al., 2003; Lake & Meck, 2013; Malapani, Deweer, & Gibbon, 2002; T. H. Rammsayer, 1993, 1997; T. H. Rammsayer & Vogel, 1992; T Rammsayer, 1989). It is possible to state that in general, timing behavior is modulated by means of dopaminergic receptors instead of the dopamine synthesis procedure. According to some animal studies using different kinds of dopamine receptors, the D2 receptor has a major role in timing (MacDonald & Meck, 2006; Meck, 1986, 1996); (Racagni, Canonico, Ravizza, Pani, & Amore, 2004). In the dopaminergic system, especially activity in the nigrostriatal⁴ rather than mesolimbic pathway possibly takes role in modulation of time, at least in temporal sensitivity in the milliseconds range.

Aging Effects on Dopamine System

Research on the relationship between neuromodulators and aging has extensively focused on the dopaminergic system due to its involvement in a variety of cognitive and motor functions including memory, time perception, reward, and movement. Owing to the high concentrations of dopamine in the striatal regions, most studies of dopamine in aging have focused on these areas. It has been observed in humans that striatal dopamine receptor activity decreased with aging. This may be due to a decline in the dopaminergic associations within striatum with increasing age, a decline in the levels of dopamine itself, a reduced number of dopamine receptors and synaptic transmission or a reduced binding potential of receptors (Nyberg & Bäckman, 2012).

⁴ Nigrostriatal pathway composes of dorsal striatum (caudate end putamen)

A positron emission tomography (PET) study revealed a significant decrease with age of D2 receptor level in caudate and putamen. This decrease was found to be steep until 30 years and slower afterward (around 0.6% per year) (Antonini et al., 1993). Although the mechanism is not clear, it is suggested that the loss of striatal neurons and/or post-transcriptional regulation of striatal neurons with increasing age would be crucial candidates (DeSouza, Kuyatt, Roth, Kochman, & Han, 2003; Sakata, Farooqui, & Prasad, 1992). An immunohistochemistry study investigated the changes in the dopaminergic system with aging, focusing on dopamine transporter protein (DAT), D1 and D2 receptors in human basal ganglia aiming to clarify their potential roles in the neuronal development of the basal ganglia (Meng, Ozawa, Itoh, & Takashima, 1999). The results of the study suggested that although D2 receptor expression decreased with increasing age, there was no apparent decrease in the number of dopaminergic neurons. Therefore, it is hypothesized that the decrease in D2 receptor expression is probably associated with post-transcriptional modifications on D2 receptor neurons. It has also been shown that D2 receptor availability in caudate and putamen declined with increasing age (Volkow et al., 1998).

One of the largest studies evaluating the relation between dopamine receptor system and human development provided evidence for a complex relation between D1 receptor density and increasing age (Seeman et al., 1987). The study reported an increase in D1 receptor density from infancy to late childhood and then a dramatic decrease throughout the remainder of the lifespan. Although there are non-human animal studies showing an age-related decrease in D1 receptor activity in striatum, suggesting a neuronal loss (Henry, Filburn, Joseph, & Roth, 1985; Morelli, M., & Di Chiara, 1990; Zhang & Roth, 1997), the results of the human study showed that D1 receptor expression but not the number of neurons decreased with aging (Meng et al., 1999), implying a post-transcriptional modification of the dopamine receptors.

Besides, a postmortem study conducted on human subjects (age range: 6-93 years) investigated D1 and D2 receptor binding in caudate and putamen (Rinne, Lönnberg, & Marjamäki, 1990). The results showed that the decrease in D1 was 3.8% and 3.7%,

and in D2 receptors 4.5% and 4.8% for caudate and putamen, respectively per decade. Another postmortem study conducted on human subjects (age range: 9 weeks to 49 years) grouped into three classes: infants, adolescents, and adults and measured D1-like receptor density and affinity in caudate and putamen (Montague, Lawler, Mailman, & Gilmore, 1999). The results indicated no change in D1 receptor affinity in both regions, a decrease in D1 receptor density in putamen but not in caudate from infancy to adulthood.

The results of the studies focusing on the relation between the dopaminergic system and aging suggest that concentration, expression and/or binding potential of postsynaptically located receptors decrease as a result of healthy aging in parallel with a decrease in the activity of the presynaptic striatal dopaminergic mechanism. Thus, it is important to investigate how our cognitive and neuronal functions are affected by age-related changes in the dopaminergic system.

2.2.2.2. Serotonin

The studies investigating the role of serotonin on various experimental tasks related to time perception have shown that involvement of serotonin in processing of temporal information is indirect. There are several studies suggesting possible effects of serotonin on timing performance in both animal and human studies. The administration of serotonin receptor agonists has resulted in a rightward shift in the bisection point of the individuals suggesting that durations were judged as shorter under the influence of the serotonin receptor agonists (Asgari et al., 2006; Body et al., 2005, 2006; Morrissey, Ho, Wogar, Bradshaw, & Szabadi, 1994). The administration of quipazine, a nonselective serotonin receptor agonist in humans led to a flat slope in the psychometric functions of the behavioral performance compared to the control group. This can be interpreted as a decrease in the temporal control of behavior (Body et al., 2004).

There are converging evidence from studies using other methods, such as neuropsychological studies of individuals with focal brain lesions, suggesting that the

dysfunction in the serotonergic pathways and transduction mechanisms do not entirely disrupt the sensitivity to time and the ability of temporal processing. Regardless, the involvement of serotonergic functioning in time perception is worth mentioning. Morrissey, Wogar, Bradshaw and Szabadi (1993) investigated the effects of lesions on the ascending serotonergic pathways on timing behavior of rats during a temporal bisection task. Although the temporal performances of rats with lesions had the same characteristics Weber fractions as those observed in sham-injected rats, they still differed with respect to the bisection point. In these rats, serotonin levels in the parietal cortex, hippocampus, amygdala, nucleus accumbens and hypothalamus of the lesioned group were found to be decreased compared to those of the control group, although there was no statistically significant difference between their noradrenaline and dopamine levels. In another study of Morrissey, Ho, Wogar, Bradshaw and Szabadi (1994), the rats with lesions in the ascending serotonergic pathways compared to sham-injected rats showed a greater variance in the response rate during a fixed-interval peak task although the peak response rate did not differ significantly between those groups. Thus, these results suggest that even the dysfunction in the serotonergic pathways and transduction mechanisms do not entirely disrupt the sensitivity to time and the ability of temporal processing, the indirect effects of serotonergic functioning in time perception is worth investigating.

2.2.2.3. Choline

Temporal memory is an important component of the time perception and cholinergic substances modify temporal estimation by affecting temporal memory rather than the internal clock (Meck & Church, 1987). Meck and Church (1987) applied a 20-second peak-interval procedure with sonic stimuli to rats injected with anticholinesterase⁵ drugs (for example, physostigmine and neostigmine as well as cholinergic receptor blockers atropine and methylatropine). Physostigmine decreased the variability of temporal discrimination and led to a dose-dependent leftward shift on time scale of

⁵ Acetylcholinesterase inhibitors which prevent destruction of the acetylcholine by the acetylcholinesterase

the temporal peak. Atropine increased the variability of temporal discrimination and the temporal rate shifted to the right on the temporal scale, in proportion to the dose administered while methylatropine produced none of these effects. Neostigmine and methylatropine were not able to pass the blood-brain barrier, hence they did not cause any change. If these results were applied to a time-domain model, physostigmine decreased the memory duration of reinforcement and increased the sensitivity to time whereas atropine had an opposite effect resulting in an increase in the memory duration of reinforcement and a decrease in the sensitivity to time. In sum, it can be said that dopamine and acetylcholine effect temporal processing in different ways. The levels of acetylcholine in the brain would therefore regulate the speed of translation of durations measured by the internal clock into the time stored in the temporal memory. Temporal learning is composed of a memory component controlled by acetylcholine, settling gradually, and an immediate component, corresponding to the internal clock which is mainly controlled by the dopaminergic system.

Furthermore, interactions between acetylcholine and dopamine have been known for a long time in the dorsal striatum which is considered as primary area involved in timing and time perception. Experimental studies and clinical evidence indicate that local cholinergic signaling has a major role in modulation of the activity and output of the striatum. Acetylcholine induces the release of dopamine by activating presynaptic nicotinic acetylcholine receptors. Upon its release, dopamine binds to D2 receptors in the striatum causing an interruption in firing of cholinergic interneurons. Therefore, the release of acetylcholine from the cholinergic interneurons in the striatum is repressed (Yan, Song, & Surmeier, 1997).

The dopaminergic nigrostriatal neuronal system is responsible for motor control and acts on the cholinergic interneurons of the striatum. The predominantly inhibitory transmitter dopamine is normally in equilibrium with the excitatory transmitter acetylcholine. The cholinergic neuron acts like an interneuron between two inhibitory substances, namely dopamine and γ -aminobutyric acid (GABA). Depending on the striatal dopamine activity, GABA inhibits the activity of dopaminergic neurons in the

substantia nigra. On the other hand, the binding of dopamine to its postsynaptic D5 receptors leads to the long-term potentiation of the excitatory synapses between corticothalamocortical afferent and cholinergic neurons (Aosaki, Miura, Suzuki, Nishimura, & Masuda, 2010). Hence there is a reciprocal relationship between dopamine and acetylcholine in basal ganglia, which indisputably affects temporal processing.

2.3. Experimental Designs Used in Timing

General paradigm used in an experimental task design specifies a fundamental difference between tasks (Richelle & Lejeune, 1984). First paradigm is retrospective in which the subject is told to reproduce a given temporal interval after having perceived it. This leads to “remembered duration” (Block & Zakay, 2006). That is, the time judgment relies on temporal memory processes. Retrospective time judgments can only be made once with a subject. Afterwards s/he will know that this experiment is about timing. Therefore, the use of retrospective paradigms is strongly restricted. The second paradigm is prospective that the subject is told to reproduce a given temporal interval before having perceived it. This leads to “experienced duration”(Block & Zakay, 2006), in which the time judgment relies on temporal perceptual processes. Prospective paradigms are much more common. They don't suffer from the problem of retrospective time judgment. They can be repeated as many times as the experimenter wishes. Several methods are used for investigation of perception of temporal intervals. These experimental procedures may be roughly divided into three categories: scaling, discrimination and differentiation (Balci, Meck, Moore, & Brunner, 2009).

The scaling methods can be presented in the following forms: verbal estimation of the duration (magnitude estimation), method of categorization (a stimulus should be assigned to a temporal category by the participants), reproduction (the subject perceives an interval and then reproduces it i.e., pressing a response key after a certain interval elapsed), ratio-setting (interpretation of a duration that is presented as a

proportion of the stimulus), production (the subject produces a specific time interval by pressing a button, after being instructed verbally about the length of the duration).

In temporal discrimination tasks, explicit temporal stimuli are presented and subjects are required to compare the two. In temporal discrimination, comparison tasks can be divided into two subcategories as forced choice and single stimulus. In forced choice, subject's duty is the identification of which one of the two stimuli is the standard duration given explicitly before. In single stimulus, short and long anchor durations are presented and participant classifies a probe stimulus as long or short. If the probe duration was different from the anchor duration and varies between short and long the task here is defined as bisection procedure. Because this is the task used in our study it will be explained in detail in the following section.

Last but not least, in temporal differentiation tasks participants give responses in time to be able to match a temporal necessity. Exemplars to this type of tasks are fixed-interval procedure, peak-interval procedure and differential reinforcement of low or high response rate. Summarizing schema of the main methods used for studying timing and time perception is depicted in Figure 2.6. In this study, we will focus on time bisection task.

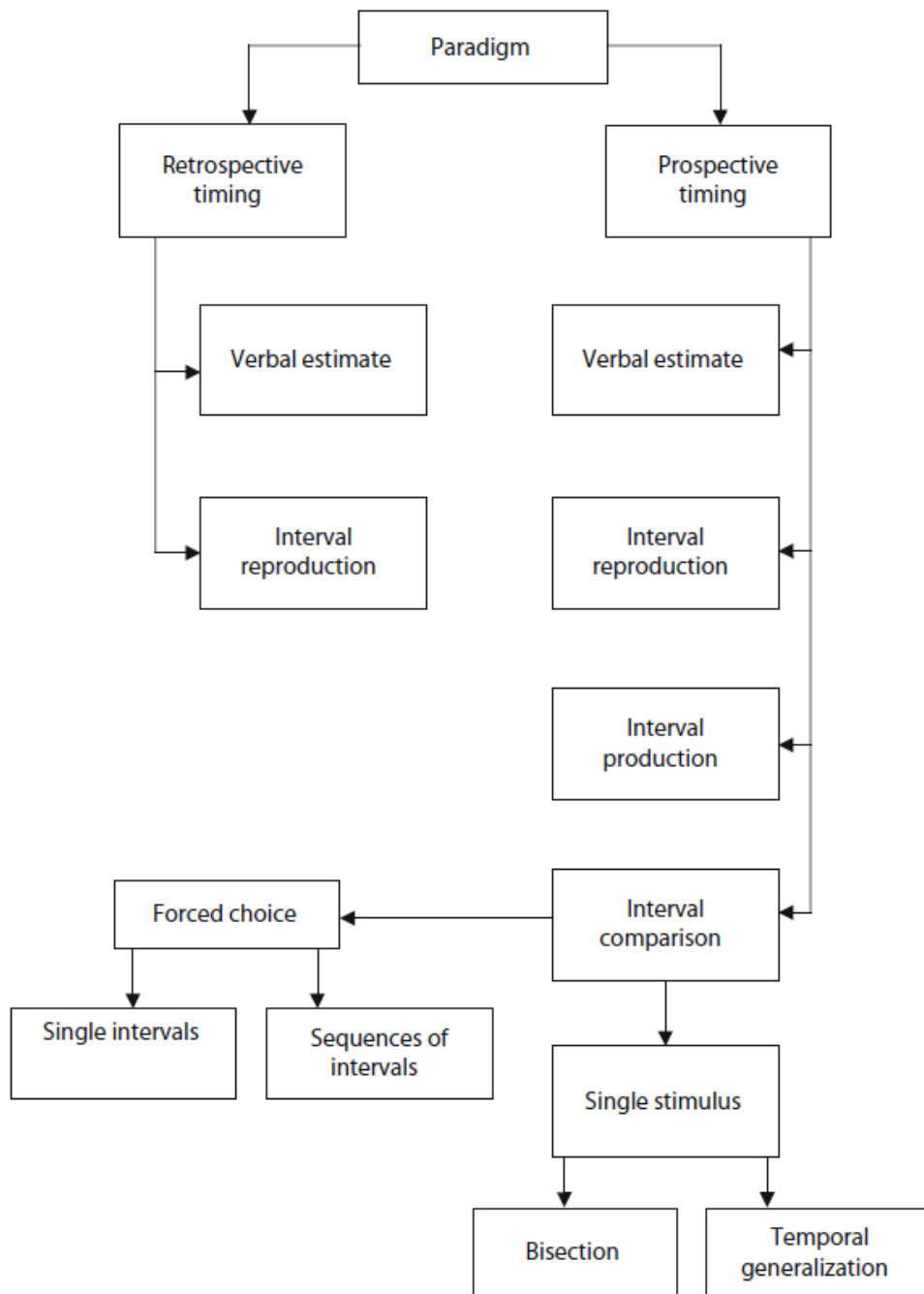


Figure 2.6. Schema of main methods used in time perception. Reprinted with the permission from Springer Nature and Copyright Clearance Center. Grondin, S. (2010). Timing and time perception: A review of recent behavioral and neuroscience findings and theoretical directions. *Attention, Perception, & Psychophysics*, 72(3), 561–582.

2.3.1. Time Bisection Task

Two common experiments for investigating subjective temporal experience are the bisection and reproduction tasks. Church and Deluty were the first scientists who used temporal bisection task in 1977 to study temporal discrimination in rats (Church & Deluty, 1977). Although a simpler version was used on humans as early as 1968 (Bovet, 1968), this task was first applied to humans in two separate pioneering works by Wearden, (1991) and by Allan & Gibbon, (1991).

In the task, human subjects are required to compare temporal stimuli to two different reference stimuli which are learned previously as “long” and “short” (Kopeck & Brody, 2010). The stimuli themselves are generally either a tone or a light presented for specific lengths of time, a red circle image in our experiments. Generally, subjects are first pre-trained on the reference stimuli, after which intermediate probe stimuli are introduced. There are some other versions of this method in which the reference stimuli are never explicitly identified (Sylvie Droit-Volet & Rattat, 2007; J. H. Wearden & Ferrara, 1995) , but still are the shortest and longest stimuli presented. Following to presentation of an intermediate probe stimulus, the subject must indicate which reference stimulus they believe it is more similar to, long or short. In the case the reference stimuli were not specifically identified, the subject must solely classify the duration as “short” or “long”.

The temporal bisection task is optimal to investigate the perception and processing of temporal information since subjects perform a number of mental operations that are time-dependent. First, the reference durations (“short” and “long”) needed to be learned and encoded in memory. Second, the length of the probe duration must be evaluated. Third, memory recall is necessary for retrieval of the values of the “short” and “long” reference durations. Finally, to be able to decide, a comparison between the probe duration and the reference durations is needed. A psychometric curve as shown in Figure 2.7 can be plotted with the help of the collected data via this task.

This curve is a representation of the duration of the stimuli versus the subject's probability of responding as "long".

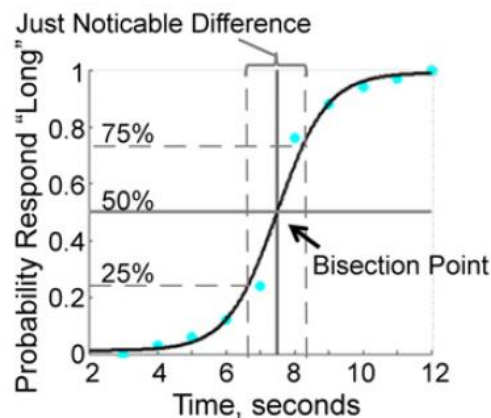


Figure 2.7. Probability of a subject responding "long" as a function of stimulus duration. The bisection point is defined as the duration which produces (50) % "long" responses. Reused with the permission from Elsevier and Copyright Clearance Center. Kopec, C. D., & Brody, C. D. (2010). Human performance on the temporal bisection task. *Brain and Cognition*, 74(3), 262–272.

A monotonic increase with respect to duration is observed in these functions which means that subjects almost never respond "long" to the shortest duration, and almost always respond "long" to the longest duration. The point that the subject's performance crosses 0.5 on the y-axis corresponds to an intermediate duration. This duration is referred to as the bisection point or point of indifference (Allan & Gibbon, 1991; Church & Deluty, 1977; Gibbon, 1981; Siegel & Church, 1984; J. H. Wearden, 1991). At the bisection point there is equal probability for subjects to call "long" or "short". Bisection point is critical since the decision making used to compare temporal stimuli to temporal values stored in memory must be equal for both options at this duration. The second measure the Difference Limen (DL) is the half the difference between the probe duration that gives rise to $p(\text{long}) = 0.75$ and that which gives rise to $p(\text{long}) = 0.25$. Finally, the third measure is Weber ratio (WR), is calculated by DL is divided by the BP (Gil & Droit-Volet, 2009) . It is an index of temporal sensitivity, which can be explained as following, the lower the WR is, the greater the sensitivity to time.

CHAPTER 3

MOTIVATION AND RATIONALE

First aim of this study was to investigate time perception in the context of aging with the hope of resolving the paradoxical results in the timing literature. Based on the factors mentioned in the background, we decided to design the behavioral experiments to minimize the attentional, motor, and memory-related demands of the task so that exclusively pure differences in time perception between two age groups, young and old adults, can be measured. The stimuli range used in our experiments was also chosen to minimize cognitive demands.

Previously, Akdoğan & Balcı (2016) investigated the effects of payoff manipulations on temporal bisection performance, but to the best of our knowledge, this is the first study to investigate time perception performances of Turkish adults in a time bisection task in terms of aging effects.

The main factors that affected our design are explained below:

1. The temporal task demanding the least cognitive capacities such as attentional load is reported as the time bisection task (S. Droit-Volet et al., 2015). To successfully make a comparison between age groups, the experiment was implemented with similar parameters used in previous aging (M. Lamotte & Droit-Volet, 2017) and developmental investigations (Zélanti & Droit-Volet, 2011).
2. During the task, an experimenter was in charge of pressing the appropriate button on the computer keyboard according to the verbal response of the old participants. This type of response recording is preferred for two reasons: 1) to minimize the performance effects derived from stress responses of old

participants who are unfamiliar with technology and 2) to minimize age-related motor decline (Charness, Fox, & Mitchum, 2011).

3. There are ample number of studies showing that counting may bias the outcomes. Chronometric counting is a critical issue, particularly considering the aging perspective, since suppressing counting ensures that observed differences are not caused by alterations in counting ability (T. McCormack et al., 1999). In a recent study that aimed to determine the best and easiest method of preventing chronometric counting in a temporal judgment task, the authors reported that the simplest and most efficient method of suppressing spontaneous counting is giving instructions to not count (Rattat & Droit-Volet, 2012). Thus, before the onset of the session, each participant was informed about this bias, and they were told that they must not count. This verbal instruction was emphasized by repeating it in written form on the computer screen.
4. We wanted to ensure that the participants' timing performances were not affected by their visual deficiencies. Therefore, a controlled experiment was designed to determine the visual acuity threshold of the participants.

Our second aim was to examine age-related morphological changes derived from healthy aging with qMRI- T₁ mapping method. The studies reporting age-related changes in iron concentration, dopaminergic system and volumetric changes of specific brain structures have been presented in the background chapter. The relationship between aforementioned alterations and relaxometry parameters is well established and global patterns observed in whole brain areas are investigated before. We analyzed whole brain data under the considerations regarding age-dependent structural changes in the brain such as atrophy.

Our final aim was to investigate whether there is an interaction between qMRI measures and timing performances of the participants. We believe that creating the connections between these behavioral and structural changes may contribute in understanding the underlying mechanisms of time perception in aging.

Hypotheses

H1: Older population will have less temporal sensitivity in temporal bisection task than younger ones.

H2: Spin lattice relaxation time (T_1) prolongation will be observed in the structures involving temporal judgements of older participants.

H3: Behavioral performance of temporal bisection task will be correlated to changes in T_1 relaxation time in both populations.

CHAPTER 4

METHOD

4.1. Behavioral Experiments

4.1.1. Participants

A total of 66 volunteers participated in study; 33 young adults (mean age \pm SD: 25.31 \pm 3.50 (range 18-35 years), 13 F, 20 M), 33 old volunteers (mean age \pm SD: 67.63 \pm 4.87 (range 60-78 years), 16 F, 16 M). Demographical information of the participants was given in Table 4.1. Young participants were recruited from the university campus via distributed fliers, social media, and e-mail. An exemplar of the study announcement is given in Appendix E. Recruitment of the old population was conducted with the help of our circle of acquaintances. This study is approved by Ankara University Clinical Research Ethical Committee (Protocol Number: 13-416-12) and Middle East Technical University Human Subject Ethics Committee (Protocol Number: 2017-FEN-059), see approval in Appendix D. All of the participants read and signed an informed consent (given in Appendix F) according to the principles of the Helsinki Declaration; they received no payment for the participation to the study but we donated seedlings on behalf of them through The TEMA Foundation (The Turkish Foundation for Combating Soil Erosion, for Reforestation and the Protection of Natural Habitats). The subjects' personal data was kept confidentially and hypothesis of the study was not explained to the participants. The only information given them was that the study was conducted to investigate time perception in different age groups. All participants had a normal or corrected-to-normal vision and reported to have no history of a neuropsychological, psychiatric disorder, or alcoholism and no use of medication affecting the central nervous system. Demographical information of the participants was given in Table 4.1.

Table 4.1. The demographical information of the subjects participated in behavioral experiments.

	Old	Young
Age (Mean \pm SD)	67.63 \pm 4.87	25.31 \pm 3.50
Gender	Female=17 Male=16	Female=13 Male=20
Years of Education (Mean \pm SD)	12.38 \pm 4.80	18.47 \pm 2.85

Additional inclusion and exclusion criteria were given as follows:

Inclusion Criteria:

- Being volunteer to participate in the study and signed informed consent form
- Basic knowledge of computer technology to be able to conduct the behavioral task.

Exclusion Criteria:

- Having any neuropsychological disease history
- Having any physical disability preventing the application of the psychological and cognitive tests (visual, hearing etc.)
- Having a metal prosthesis (or pacemaker)
- Having claustrophobia (the last two exclusion criteria were considered for MR imaging).

4.1.2. Neuropsychological Tests

Mini-Mental State Examination (MMSE)

Since memory processes and cognitive state is important for our task, the Mini Mental State Examination (MMSE) (Folstein, Folstein, & Mchugh, 1975) (for Turkish version see Gungen, Ertan, & Eker, 2002) was administered to the old participants. This is a 30-point questionnaire which is utilized commonly in clinical and research settings for the purpose of measuring cognitive impairment. It is extensively used in medicine to screen dementia and there is no time restriction of the test. MMSE is composed of two sections, the questions in the first section is responded vocally and testing areas are orientation (10 points), memory (3 points), and attention (5 points); the maximum score is eighteen. The second section covers the ability to naming, following verbal and written commands, writing a sentence spontaneously, and copying a complex polygon; the maximum score of this part is twelve. The maximum total score of MMSE is 30. Any score greater than or equal to 24 points (out of 30) indicates a normal cognition. Below this, scores can indicate severe (≤ 9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment. See Appendix B, for full version of MMSE.

The cut-off score of 24 and all of our participants satisfied this criterion indicating that they didn't suffer from dementia. The average MMSE score of old volunteers is $26.34 \pm .46$ pointing out that all of the participants demonstrated a normal cognition.

Geriatric Depression Scale (GDS)

This scale is designed specifically for rating depression in the elderly (Yesavage et al., 1983); validation and the reliability in Turkish population is conducted before (Ertan & Eker, 2000). GDS is composed of 30 questions related with depression regarding last week (given in Appendix C). The GDS was given orally and participants were asked to answer as yes/no. The administration of the test is about 5 min. Each depressive answer was counted up 1 and the final score is the tally of the number of depressive answers with the following scores indicating depression:

- 0-10 No depression
- 11-13 Suggestive of a mild depression
- 14+ Suggestive of severe depression

The average GDS score of old participants is $5.28 \pm .84$ and none of the volunteers exceed the mild or moderate depression threshold. Hence none of our old participants are excluded due to suffering from depression.

4.1.3. Material

All the participants were tested individually in a quiet room, either in their homes or in an office at university campus. They were seated in front of a PC (ASUS K55VJ – SX077D) with an approximate 40 cm distance between, the experimental stimuli were presented via SuperLab 4.0 software (Abboud, H., W. Schultz, 2006). Computer keyboard was used for recording of the responses.

In time bisection task, to be able to make a comparison, the same stimulus range was used in the experiment conducted by Zélanti and Droit-Volet (2011). During the task, an experimenter was in charge of pressing the appropriate button on computer keyboard according to the verbal response of the elderly participants ('S' for short or 'L' for long). This type of response recording is preferred to minimize the performance effects resulting from both stress responses of old participants who might be unfamiliar to modern technologies and might have age-related motor disorders. A red circle (6 cm in diameter) is shown in the center of the computer screen on a white background as a stimulus subjected to timing. A 500-ms feedback is presented after each short and long anchor durations. A positive feedback in the form of a tick image in the case of correct responses, and a negative feedback in the form of a cross image was given in incorrect condition. Experimenter told the participants that they should consider these kinds of feedbacks because participants are expected to learn the task. Before the onset of the session, each participant was informed about counting may bias experimental outcome, and they were told that they must not count. In addition to the verbal instruction, this caution was repeated on computer screen. The visual

representations of the stimulus, feedbacks used in the task and instructions are presented in Figure 4.1.

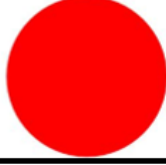


a. 	b. 	c. 
d. Çalışmamıza hoşgeldiniz. Deneme bölümü başlıyor. Ekranda kırmızı bir daireyi kısa ya da uzun süre göreceksiniz. Bu aşamada sadece uyararı öğrenmenizi bekliyoruz. Bir cevap vermeniz gerekmiyor. Başlamak için herhangi bir tuşa basınız.	İkinci deneme bölümü başlıyor. Kırmızı daire ekranda kısa süre görüldüyse cevap olarak 'Ş', Uzun süre görüldüyse 'L' tuşuna basınız. Cevaplarınıza olumlu ya da olumsuz geribildirim verilecektir. Başlamak için herhangi bir tuşa basınız.	
Kısa mı uzun mu?	Çalışma başlıyor. Kırmızı daire ekranda kısa süre görüldüyse cevap olarak 'Ş', Uzun süre görüldüyse 'L' tuşuna basınız. Sadece bazı cevaplara olumlu ya da olumsuz geribildirim verilecektir.	

Figure 4.1. Time bisection task design: a. Stimulus, b. Positive Feedback, c. Negative Feedback, d. Instructions.

4.1.4. Procedure

4.1.4.1. Time Bisection Task

Short and long anchor durations were 1.25 s and 2.5 s, respectively, and the probe durations are composed of 1.25, 1.458, 1.667, 1.875, 2.083, 2.292 and 2.5 s. A session included three phases: a pre-training, a training, and a testing phase. In the pre-training phase, the two anchor durations were presented in sequence: three short and three long

anchor durations. No responses were expected from the participant at this stage; experimenter introduced the durations by stating ‘This circle appears on the screen for a short/long time’. In the training phase, the participants learned to respond by pressing ‘S’ for short and ‘L’ for long durations. Two blocks of 10 trials were given, each including five short and five long stimuli. An appropriate feedback was given after each response in this phase. The inter-trial interval varied between 0.5 and 2 s. If the participant got more than 70 % correct response in the second trial block, the testing phase was presented (all of our participants satisfied this criterion).

Aforementioned procedure was used in the testing phase with an addition of probe durations and the feedbacks were given only for the shortest and longest durations. Testing phase was composed of 10 blocks of 7 trials each (70 testing trials): one trial for each S and L anchor durations and one trial for each of the five intermediate durations. The presentation of these trials was randomized in each block. Time bisection task design was summarized in Figure 4.2.

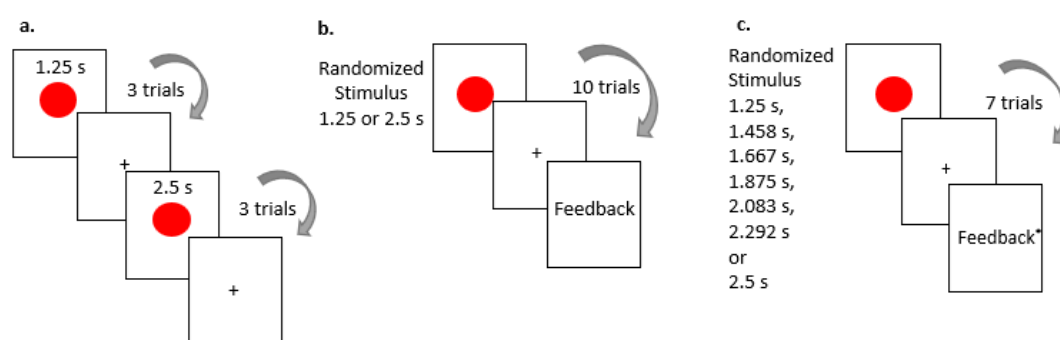


Figure 4.2. Time Bisection Task Design. a. Pre-training Phase: 1 block, b. Training Phase: 2 blocks, c. Testing Phase: 10 blocks. * Feedbacks in testing phase were given only in anchor durations (1.25 and 2.5 s).

4.1.4.2. Visual Acuity Task

Since our study includes visual stimuli, we wanted to investigate whether there is a difference in the visual ability of participants across age groups and ensure that participants' timing performance is not affected by their visual condition. This control experiment is designed to determine the visual acuity threshold of the participants. The red circle used in time bisection experiment was modified by adding transparency

at various levels. In total, 29 stimuli were created via a MATLAB code with varying transparency addition [0.004 (most transparent), 0.008, 0.012, ..., 0.092, 0.096, 0.100, 0.40, 0.70, 1 (no transparency added)]. Each stimulus was demonstrated for 1.25 s then; participants were asked to decide whether they saw a colorful circle or not. If the answer was 'yes', they were told to press '+', otherwise, press '-' and no feedback was given. Each participant completed 5 blocks of 29 trials. As in the previous experiment, the trial presentation was randomized within each block.

4.1.4.3. Subjective Passage of Time Questionnaire

Lastly, the participants were asked to complete a questionnaire titled, "Speed of Time" developed by Wittmann and Lehnhoff (2005). This is a six-item questionnaire all using their five-point rating scale (very slowly [-2], slowly [-1], neither fast nor slow [0], fast [1], and very fast [2]). The Items were translated from English to Turkish by authors, and recommendations of a field expert for face validity were considered. The items of the questionnaire were given below:

2. *How fast does time usually pass for you?*
3. *How fast do you expect the next hour to pass?*
4. *How fast did the previous week pass for you?*
5. *How fast did the previous month pass for you?*
6. *How fast did the previous year pass for you?*
7. *How fast did the previous 10 years pass for you?*

4.2. Brain Imaging

4.2.1. Participants

A total of 63 participants were volunteer to participate in the study, however 1 young and 2 old subjects were excluded from the study because of their claustrophobia. Hence, a total of 60; 30 young (Mean=26.36, SD=2.69, 12 F, 18 M) and 30 old (Mean=67.46, SD=4.89, 16 F, 14 M) subjects participated in the study, for detailed information see Table 4.2.

Table 4.2. The demographical information of the subjects participated in MR experiment.

	Old	Young
Age (Mean \pm SD)	67.46 \pm .4.89	26.36 \pm .2.69
Gender	Female=16	Female=12
	Male=14	Male=18
Years of Education (Mean \pm SD)	12.4 \pm .4.95	18.32 \pm 2.77

4.2.2. Procedure

MRI data were collected in UMRAM MR Center (National Magnetic Resonance Research Center), Bilkent University. The subjects were instructed to lie in the scanner and not fall asleep. The scan lasted about 20 minutes.

High resolution 3D anatomical brain images were collected Magnetization Prepared Rapid Gradient Echo (MPRAGE) protocol (TR=2500 ms, TE=3.16 ms, Bandwidth=199 Hz/Pixel, matrix 256*256, Slice Thickness 1mm, 256 slices, FOV=256*256 (axial), Number of Averages=1). Then 4 brain images with four different flip angles (3°, 5°, 15°, 30°) that adhered to the same imaging coordinates with the MPRAGE sequence were collected with Fast Low Angle Shot (FLASH) sequence (TR= 20ms, TE=4.15 ms, Bandwidth=199 Hz/Pixel, matrix 256*256, with Slice Thickness 3 mm, 44 slices, FOV=256*256 (axial), Number of Averages=1). These protocols are chosen on purpose because they are widely available and allow for estimation of T₁ tissue characteristics which we wanted to investigate.

4.2.3. Data Processing

4.2.3.1. Preprocessing

Making Deoblique: FLASH images with varying flip angles (3,5,15, and 30 degrees) were collected sequentially in about 10 mins. This procedure is susceptible to head motion and since the field of view (FOV) adjustment was conducted manually before MRI scan session, the MR images of the same participant could differ in orientation. To compensate this misalignment, AFNI program 3dWarp used. Linear warping was chosen during spatial transformation of the dataset. Hence, we have properly registered images to compare results across scanning sessions.

Alignment: Both FLASH and MPRAGE images were aligned to the standard stereotaxic space- Talairach-Tourneux (TLRC) coordinates. A script was written to transform these anatomical datasets to match TT_N27 template in TLRC space. AFNI program auto_tlrc with 12-parameter affine transform was used for registration of FLASH images, to have a better convergence shift-rotate-scale transform and maximum iteration of 500 were used for the alignment of the MPRAGE images.

Skull Stripping: The output of the auto_tlrc program was a dataset whose non-brain parts of the brain extracted.

4.2.3.2. T₁ Mapping

The MR signal consists of several components. T₁ is the longitudinally decaying component of the magnetization after RF pulse excitation with respect to time in the MR signal. The interactions of protons and their surrounding in a magnetic field affect T₁ relaxation time. By estimating T₁ characteristics and using T₁ maps instead of intensity values, contrast between brain tissue classes can be increased. Variable flip angle (VFA) method is used for the purpose of T₁ mapping of whole brain such that at least 3 images should be gathered with three different contrasts. The different flip angle choices provide images with different contrast due to varied relaxation times. The four FLASH images collected with different flip angles (3°, 5°, 15°, 30°) are demonstrated in Figure 4.3. The VFA approach was shown to be a practical alternative to conventional methods, providing better precision and speed.

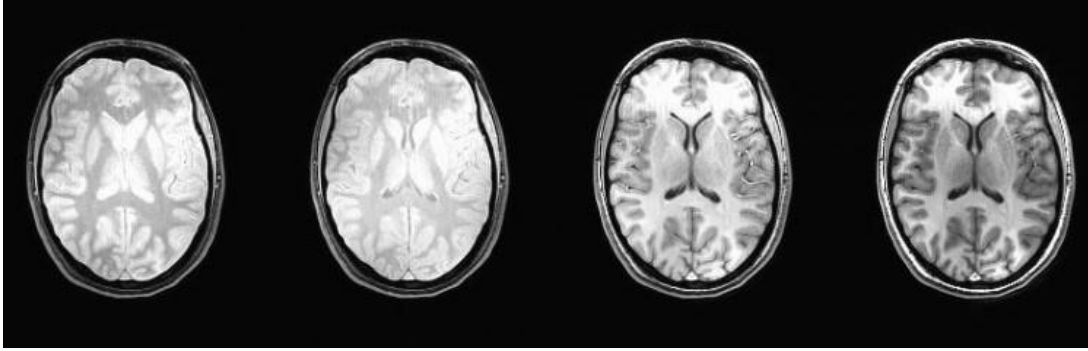


Figure 4.3. The raw MR image of a young participant on a mid-slice acquired with different flip angles (From left to right: FA=3°, FA=5°, FA=15°, FA=30°).

FLASH is an appropriate sequence for VFA method (Fischl et al., 2004). The intensity value $I(x, y, z)$ observed in the (x, y, z) voxel of a FLASH image can be written in terms of tissue characteristics [magnetization transfer constant (M_0), longitudinal relaxation time (T_1) and transverse relaxation time (T_2)] and scanning parameters [repetition time (TR), echo time (TE) and flip angle (α)] as follows:

$$I(x,y,z)=\frac{M_0(x,y,z) e^{-TE/T_2} \sin(\alpha)(1-e^{-TR/T_1})}{(1-\cos(\alpha) e^{-TR/T_1})} \quad (4.1)$$

The aim is to use the multiple FLASH images for estimating T_1 tissue value voxel wise. Then, segmentation or other automatic image processing procedures can be based on T_1 maps instead of intensity value of the voxel. For really small α values (e.g. $\alpha=3^\circ$) $\cos(\alpha)$ approaches to 1 and the equation (4.1) can be reduced as follows (Buxton, 2009):

$$I(x,y,z)=M_0(x,y,z) e^{-TE/T_2} \sin(\alpha) \quad (4.2)$$

This way, the intensity value of $\alpha=3^\circ$ image is described as the constant $c=M_0(x, y, z) e^{-TE/T_2^*} \sin(3)$. Therefore, the first part of the eq. (4.1) can be determined just by using the image with FA 3° .

The equation can be rewritten as follows:

$$I_\alpha(x,y,z)=\frac{c(\sin(\alpha)/\sin(3))(1-e^{-TR/T_1})}{(1-\cos(\alpha))e^{-TR/T_1}} \quad (4.3)$$

In this equation, $I_\alpha(x, y, z)$ is the intensity value observed in FLASH images with 5° , 15° and 30° flip angles, respectively and c is acquired from the image with $\alpha = 3^\circ$. Scanning protocol provides various parameters, including TR hence, we need to find T_1 value which is the only unknown parameter by using 3 equations derived from 3 images which is an over-determined case. Aforementioned method is implemented in MATLAB (The Mathworks Inc., 2015), (code is given in Appendix G). We can compute the T_1 value with least squares estimation method as follows:

According to literature T_1 ranges between 0-4000 ms. The intensity value for $\alpha=5^\circ$, 15° and 30° is computed based on eq. (4.3) for all of the candidate T_1 values. Then, computed theoretical I_α for each T_1 and measured real I_α in image is subtracted and squared. The T_1 value of the I_α which has the smallest error is assigned as the T_1 value of that particular voxel (LSE fit). Registered FLASH images were converted to NIfTI data format which to make it easier to interchange data between different analysis packages (MATLAB, AFNI and FSL packages in our study).

Alignment of T_1 Maps: During switching between different environments the misalignment of the T_1 maps occurred. Hence, we applied extra alignments to T_1 maps in such a way that by using a general alignment script (align_epi_anat.py) (Saad, 2009) of AFNI to align these maps with anatomical data (MPRAGE). This Python script combines motion correction, alignments and Talairach transformations into a single transformation. Several kinds of outcomes (e.g. datasets, motion parameters and transformation matrices) are generated by this program that can be used for alignment of other datasets later. Thus, we have used MPRAGE dataset that has been aligned to

Talairach space as ‘anatomical parent’ and aligned T_1 maps to MPRAGE. Also, parameters were chosen based on removing giant movement and aligning centers of the two datasets.

Segmentation: As a preliminary preparation step for ROI analyses MPRAGE images were segmented into three tissue types White matter (WM), Gray matter (GM) and Cerebrospinal Fluid (CSF) classes via FMRIB's Automated Segmentation Tool (FAST) (Y. Zhang, Brady, & Smith, 2001). Since T_1 maps were synthetically produced, package programs like FSL failed to produce segmented volumes. Therefore, we have used segmented outputs of the MPRAGE dataset for masking T_1 maps which fit perfectly because we have aligned T_1 maps to MPRAGE dataset, previously. These segmented datasets include binary brain mask images for usage as tissue type masks in such a way that WM and GM masks were used to calculate average T_1 values in the predefined ROIs for each tissue types, respectively. CSF mask was utilized with the aim of removing CSF especially in cortical and subcortical areas due to age-related atrophy.

4.2.3.3. ROI Analyses

ROI Creation: CA_N27_ML atlas (Eickhoff-Zilles macro labels from N27 in Talairach TT_N27 space) was chosen for masking the atlas region. This atlas has a total of 115 defined brain regions (12 ROIs from subcortical, 78 ROIs from Cortical and 25 ROIs from Cerebellum). We have measured average T_1 values a total of 218 regions (12 regions from CSF removed subcortical area, 78 for each WM and GM masked cortical area and 25 for each WM and GM masked cerebellum area). We have preferred to analyze the T_1 variations in these regions separately for WM and GM to be able to get rid of partial volume effects (PVE) observed in these regions and minimize segmentation and registration errors. Figure 4.4 demonstrates basal ganglia which plays a crucial role in timing tasks. 6 ROIs constituting basal ganglia (bilateral putamen, caudate and globus pallidus) were combined and overlaid on a T_1 map of a young participant for a visual exemplar, actually these six ROIs were analyzed separately.

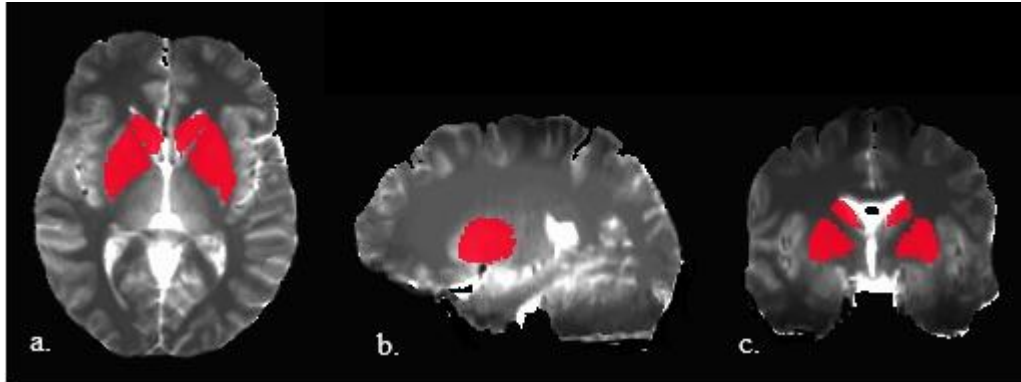


Figure 4.4. Basal Ganglia structures were overlaid on a T_1 map. a. axial view, b. sagittal view, c. coronal view.

Signal Measurement: After creation of new ROI datasets, we used AFNI program ‘3dmaskave’ to compute average of all voxels in T_1 maps matching with ROI mask. Figure 4.5 presents some of the exemplar steps of data processing. Figure 4.5.a. demonstrates skull striped, aligned to Talairach space and deobliqued MPRAGE image. This image was used as a template for segmentation of three tissue classes and then tissue specific mask images were obtained that can be seen in Figure 4.5.b. GM and WM T_1 maps were acquired by multiplication with these binary masks for every ROI defined in CA_N27_ML atlas on Cerebellum and Cortical area (see Figure 4.5.c). CSF mask was used to removal of CSF in subcortical area, this is especially vital for the processing of old participants’ brain images that have ventricular enlargement and atrophy.

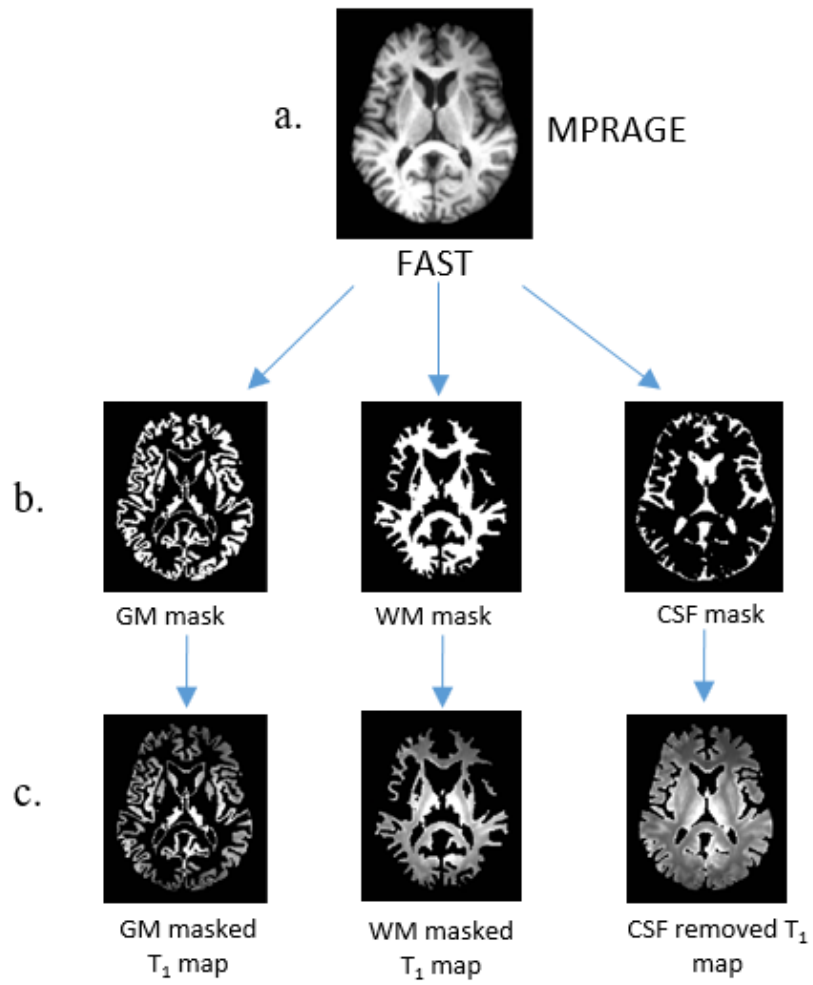


Figure 4.5. Masking process of T_1 maps according to tissue types.

CHAPTER 5

RESULTS

5.1. Behavioral Experiments

5.1.1. Time Bisection Task

The probability of the long responses was plotted against stimulus duration, and the resulting psychophysical function is presented in Figure 5.1. The psychophysical function of both age groups looks sigmoidal and closely similar to those previously conducted in this experimental paradigm (Lamotte, 2017) which verifies that they successfully fulfilled the task. According to Kolmogorv-Smirnov test data were non-normally distributed ($p \leq 0.05$). A Mann-Whitney U test depicted that there is no significant age-related difference in probability of long responses of each duration ($p \geq 0.05$). For a further analysis, Bisection Point (BP), Weber Ratio (WR) and Difference Limen (DL) were calculated by fitting a logarithmic function to the psychophysical functions from individual participants with a MATLAB (Mathworks – Natick, MA) code via psignifit 4 software (Schütt, 2016). One young participant was excluded from the study since the fit was not significant, and one old participant was also excluded from the subsequent analyses due to her failure in reaching 70% success criterion in the second training block.

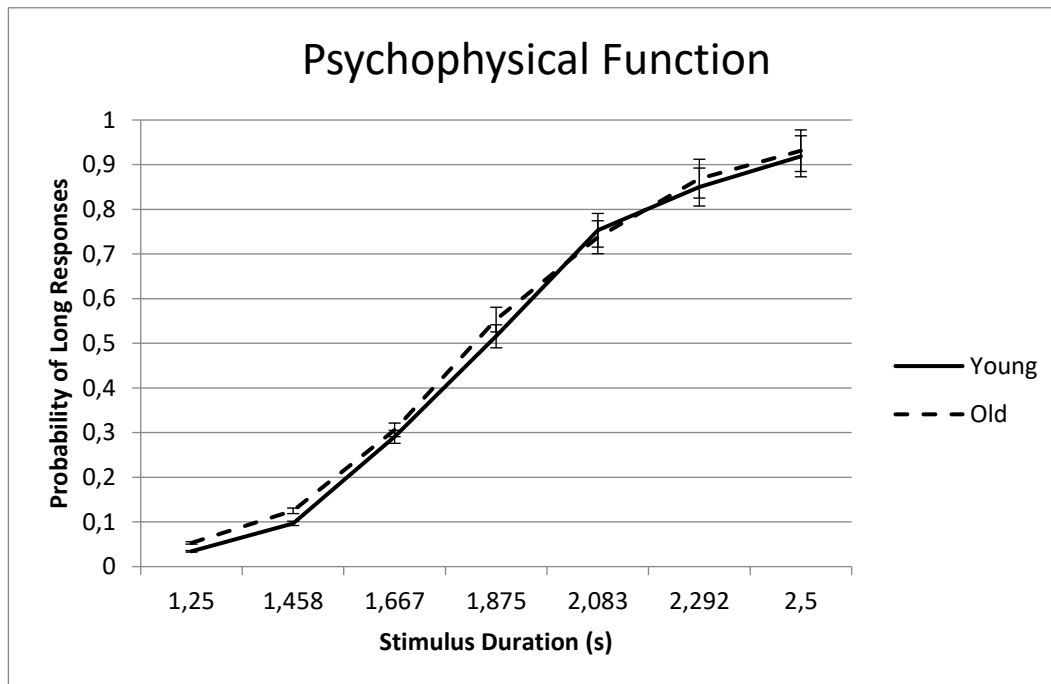


Figure 5.1. Proportion of long responses plotted against stimulus durations for the different duration ranges and for the old and the young adults.

The BP (or the point of subjective equality, PSE) is regarded as the fundamental measure in bisection studies (Meck, 1983, 1996) and can be defined as the stimulus duration that the participants gave equal number of short and long responses. In other words, it's a measure of timing accuracy. By investigating curve-fitted data of each participant, the signal duration corresponding to 50% of the long responses ($p(\text{long})=0.5$, is the probability of a subject to respond 'long' with the probability of 50%) was calculated with the help of the above-mentioned MATLAB code and reported as BP. Similarly, using the curve fitted data DL, which is a measure of variability, was calculated via subtracting stimulus duration corresponding to 25% of responses evaluated as 'long' from the stimulus duration at which 75% of the 'long' responses and halved. DL can also be defined as absolute temporal sensitivity and an indicator of the smallest difference in stimulus duration which can be discriminated reliably in the pool of a stimuli set. Hence the larger DL corresponds to the lower sensitivity and vice versa. WR, as another closely related measure, can be defined as relative temporal sensitivity and is calculated by dividing DL to BP. The lower WR is

an index of the greater sensitivity to time. Since DL is assumed to increase with BP (according to Weber’s law), WR is expected to remain constant with varying anchor durations. Thus, WR is a good metric appropriate for the comparison of variability in timing amongst different anchor durations in various studies. Outcomes of the time bisection experiment are depicted in Table 5.2 and Figure 5.2.

A Kolmogorov-Smirnov test indicated that normality assumption was violated ($p \leq .05$) hence, Mann-Whitney U test was preferred. BP of young participants ($Mdn=1.885$) did not differ significantly from old subjects ($Mdn=1.873$), $U=553$, $z=.551$, *ns*. Also, WR of young participants ($Mdn=.098$) did not differ significantly from old subjects ($Mdn=.0984$), $U=524$, $z=.161$, *ns*. Similarly, DL of young participants ($Mdn=.196$) did not differ significantly from old subjects ($Mdn=.183$), $U=534.5$, $z=.302$, *ns*.

In order to analyze further, participants were categorized into four groups as in McCormack’s study (1999): young (18-25), middle young (26-35), young-old (60-70) and old-old (71-80). None of the variables exhibited significant effect of aging through these age categories, under these new conditions, as well. Table 5.1 Time bisection experiment outcomes of the participants.

Table 5.1. Time bisection experiment outcomes of the participants.

	Old	Young
BP	1.867±.032	1.881±.020
WR	.107±.008	.109±.008
DL	.198±.014	.206±.016

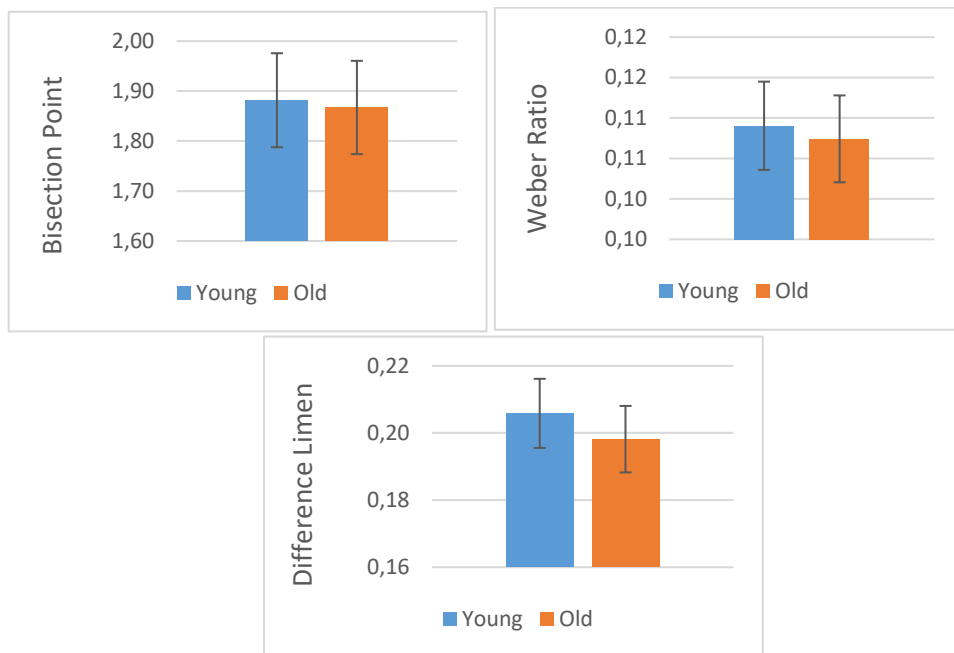


Figure 5.2. Bisection point, Weber Ratio and Difference Limen of young and old participants.

5.1.2. Visual Acuity Task

Psychometric functions were calculated for each subject in the same way defined for time bisection experiment, and a logarithmic function fitted. The probability of saying ‘yes’ was plotted against stimulus range. BP was calculated on curve-fitted data, and this value was assumed as the visual acuity threshold. A Kolmogorov-Smirnov test demonstrated that data was non-normally distributed ($p \leq .05$), Mann-Whitney U test was conducted. Visual acuity threshold of young participants (Mdn=.0256) did not differ significantly from old participants (Mdn=.0297), $U=397$, $z=-1.544$, ns. This was also replicated in the four age categories case. There was no age effect on visual acuity threshold, which means that young and old participants’ vision did not differ as they were reported normal or corrected to normal.

5.1.3. The Speed of Time Questionnaire

The items in this questionnaire were rated in a five-point likert scale. The measurement level of the likert scales are ordinal and they should be analyzed with non-parametric tests (Jamieson, 2004). An Independent Samples Median test showed that there was a significant trend of higher scores in Item 2 ('How fast do you expect the next hour to pass?') for young subjects ($Mdn=1$) than old ones ($Mdn=0$), $\chi^2=7.570$, $p\leq.01$.

When the items are compared according to 4 age groups; Independent Samples Median test demonstrated a significant difference among young ($Mdn=1$), middle-young ($Mdn=1$), young-old ($Mdn=1$) and old-old ($Mdn=1$) for Item 1 ('How fast does time usually pass for you?'), $\chi^2=10.353$, $p\leq.05$ (Bonferroni correction was used). Item 2 also rated significantly different among the age groups young ($Mdn=1$), middle-young ($Mdn=1$), young-old ($Mdn=0$), old-old ($Mdn=0$), $\chi^2=9.339$, $p\leq.05$ (Bonferroni correction was used).

The factorability of six items was examined using Principal Component Analysis and a rotation method of Varimax with Kaiser Normalization. The sampling adequacy was verified with the Kaiser-Meyer-Olkin measure, $KMO=.646$. According to Bartlett's test of sphericity $\chi^2(15) = 60.499$, $p\leq.001$, correlations between variables were sufficiently large for PCA. Overall analyses yielded two factors: Item 1 and 2 constituted a factor related to present time perception. The other four items regarding past time information formed a second factor. Two components had eigenvalues over than Kaiser's criterion of 1 and they jointly explained 56.05% of the variance. Additionally, the reliability of the questionnaire with the value of Cronbach's alpha = 0.668.

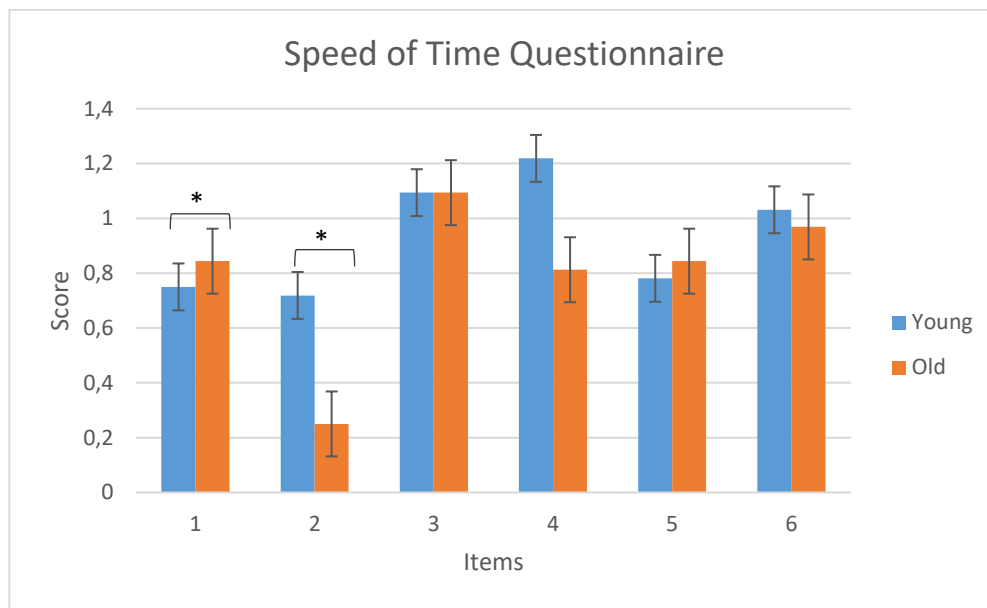


Figure 5.3. Mean ratings of the young and older adults on Items 1–6 of the speed-of-time scale (Appendix A). The values represent time passing: very slowly [-2], slowly [-1], neither fast nor slow [0], fast [1], and very fast [2].

5.1.4. Correlation Analysis

There is a negative correlation between age (in years) and education (in years) ($r(64) = -.469, p \leq .00$). As the correlation indicates, education level of the older subjects is lower than the younger ones. Also, a negative correlation between Item 2 and age (in years) was observed ($r(64) = -.247, p \leq .05$) which means that as the participants get older they reported an expectation of a slower passage of time for the next hour than the younger ones. DL, and BP are not correlated with age (in years) and also education (in years). Also, a regression analysis was conducted to investigate the effect of age and education together on BP, WR, and DL that was also insignificant. There is no correlation between BP, WR, DL and GDS, MMSE.

5.2. MRI Analysis

5.2.1. Signal Measurements in Timing Structures

Subcortical area: The normality assumption was checked with Kolmogorov-Smirnov test and this test indicated that the T_1 values measured in subcortical area have a normal distribution ($p \geq .05$). Independent Samples t-test demonstrated that average T_1 value in bilateral hippocampus, thalamus and caudate of old group were significantly higher than of younger counterparts ($p \leq .05$), for detailed information see Table 5.2. The T_1 values of timing structures measured in subcortical area were plotted against age and depicted in Figure 5.4.

Table 5.2. Average T_1 values measured in Subcortical Area

ROI	Age Group	df	T_1 (ms) (Mean \pm SD)	Test Statistics (t)	Sig.
Left Hippocampus	Old	59	1491.10 \pm 107.99	-2.59	p=.012
	Young	59	1424.64 \pm 92.02		
Right Hippocampus	Old	59	1455.62 \pm 127.32	3.183	p=.002
	Young	59	1362.93 \pm 98.78		
Left Caudate	Old	59	1384.08 \pm 99.54	-2.345	p=.023
	Young	59	1327.77 \pm 87.82		
Right Caudate	Old	59	1307.90 \pm 96.70	-3.775	p=.000
	Young	59	1221.27 \pm 82.14		
Left Thalamus	Old	59	1451.06 \pm 88.62	-5.471	p=.000
	Young	59	1337.97 \pm 72.25		
Right Thalamus	Old	59	1479.51 \pm 94.39	-6.673	p=.000
	Young	59	1336.14 \pm 72.30		

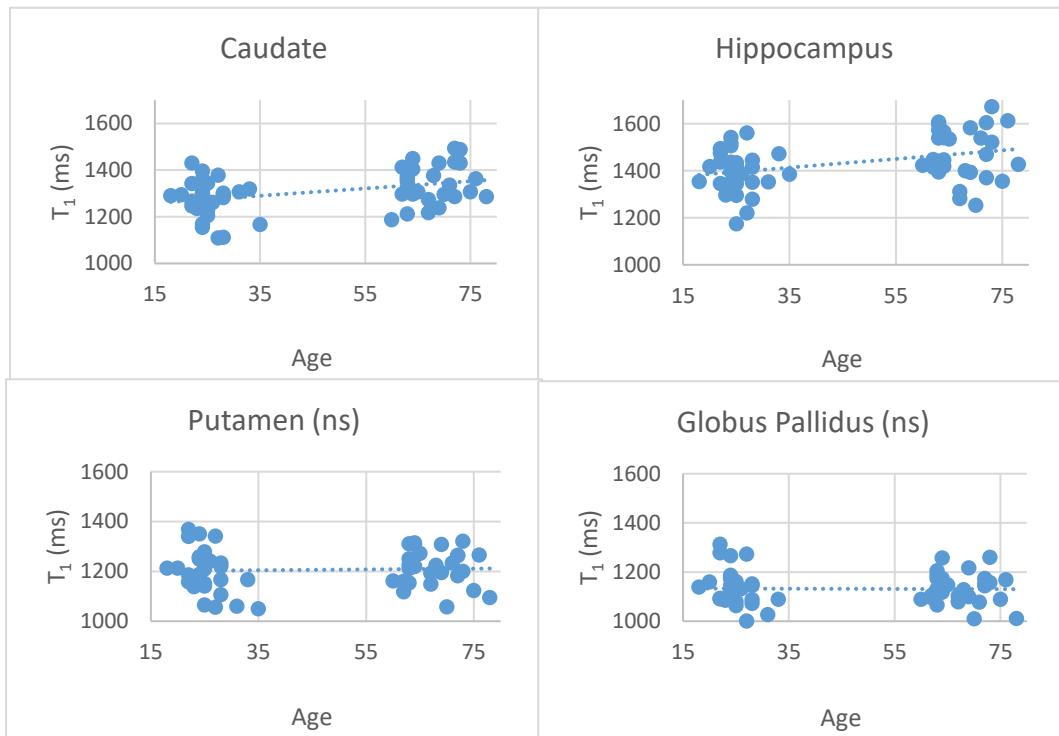


Figure 5.4. T_1 relaxation times of subcortical timing structures were plotted against age. Age-related difference in T_1 measured in putamen and globus pallidus was not significant (ns).

WM Regions in Cerebellum: A Kolmogorov-Smirnov test indicated that T_1 values measured in WM regions in Cerebellum did not have a normal distribution ($p \leq .05$). A Mann-Whitney U Test was conducted to compare average T_1 values in WM ROIs measured in Cerebellum across two age groups. The average T_1 value measured in left Cerebellum IX, bilateral Cerebellum X and Cerebellar Vermis u 4 5 of the old participants were significantly higher than in of young participants (see Table 5.3).

Table 5.3. Average T_1 values measured in WM Regions in Cerebellum

ROI	Age Group	df	T_1 (ms) (Median)	Test Statistics (U)	Sig.
Left Cerebellum IX	Old	59	543.45	599	p=.027
	Young	59	449.02		
Right Cerebellum X	Old	59	644.16	583	p= .010
	Young	59	542.85		
Left Cerebellum X	Old	59	624.00	535	p=.034
	Young	59	530.12		
Cerebellar Vermis u 4 5	Old	59	1385.64	584	p=.047
	Young	59	1332.61		

GM Regions in Cerebellum: A Kolmogorov-Smirnov test points that T_1 values measured in this region did not normally distributed ($p \leq .05$). An Independent-Samples Mann-Whitney U test indicated significant age-related differences in average T_1 measurements in 9 GM regions of Cerebellum. The average T_1 values of old participants measured in bilateral Cerebellum III, Cerebellum IV V, Cerebellum X, Cerebellar Vermis u 4 5 and Cerebellar Vermis u 9 were significantly greater than of younger ones (for detail, see Table 5.4). The T_1 values measured in both WM and GM regions of cerebellum X were plotted against age and depicted in Figure 5.5.

Table 5.4. Average T_1 values measured in GM Regions in Cerebellum

ROI	Age Group	df	T_1 (ms) (Median)	Test Statistics (U)	Sig.
Left Cerebellum III	Old	59	1655.57	603	p=.023
	Young	59	1543.77		
Right Cerebellum III	Old	59	1679.65	596	p=.030
	Young	59	1561.21		
Left Cerebellum IV V	Old	59	1525.04	655	p=.002
	Young	59	1446.18		
Right Cerebellum IV V	Old	59	1583.41	598	p=.028
	Young	59	1494.00		
Left Cerebellum X	Old	59	783.60	619	p=.012
	Young	59	646.73		
Right Cerebellum X	Old	59	915.57	643	p=.004
	Young	59	656.36		
Cerebellar Vermis u 3	Old	59	1917.77	609	p=.018
	Young	59	1816.37		
Cerebellar Vermis u 4 5	Old	59	1804.00	595	p=.031
	Young	59	1741.17		
Cerebellar Vermis u 9	Old	59	751.34	589	p=.039
	Young	59	657.854		

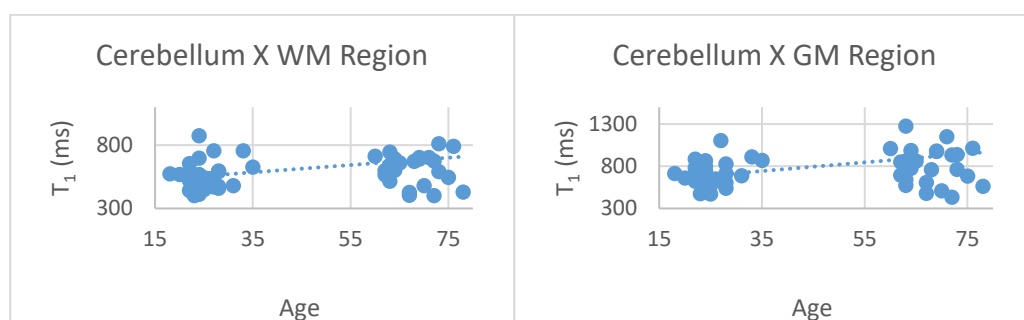


Figure 5.5. The T_1 values measured in both WM and GM regions of cerebellum X were plotted against age.

WM Regions in Cortex: A Kolmogorov-Smirnov test was conducted and indicated that T_1 values in this area were non-normally distributed ($p \leq .05$). A Mann-Whitney U test showed significantly greater average T_1 values of old group measured in bilateral pre-central Gyrus, right Superior Frontal Gyrus, right Middle Frontal Gyrus, right Inferior Frontal Gyrus pars Triangularis and bilateral Inferior Frontal Gyrus pars Opercularis than of younger group (detailed information in Table 5.5). The T_1 values of timing structures measured in WM regions of cortex were plotted against age and depicted in Figure 5.6.

Table 5.5. Average T_1 values measured in WM Regions in Cortex

ROI	Age Group	df	T_1 (ms) (Median)	Test Statistics (U)	Sig.
Left Precentral Gyrus	Old	59	741.73	705	p=.001
	Young	59	672.31		
Right Precentral Gyrus	Old	59	712.76	663	p=.004
	Young	59	643.42		
Right Superior Frontal Gyrus	Old	59	636.20	647	p=.009
	Young	59	605.09		
Right Middle Frontal Gyrus	Old	59	722.59	627	p=.019
	Young	59	684.03		
Right Inferior Frontal Gyrus Pars Triangularis	Old	59	810.68	642	p=.011
	Young	59	762.60		

Table 5.5. Average T₁ values measured in WM Regions in Cortex Cont.

ROI	Age Group	df	T ₁ (ms) (Median)	Test Statistics (U)	Sig.
Left Inferior Frontal Gyrus Pars Opercularis	Old	59	911.00	631	p=.017
	Young	59	864.57		
Right Inferior Frontal Gyrus Pars Opercularis	Old	59	870.90	678	p=.002
	Young	59	803.00		
Left Rolandic Operculum	Old	59	985.78	606	p=.042
	Young	59	952.02		
Right Rolandic Operculum	Old	59	965.51	658	p=.005
	Young	59	896.13		
Left Supplementary Motor area (SMA)	Old	59	557.00	670	p=.003
	Young	59	492.03		
Right Supplementary Motor area (SMA)	Old	59	595.65	697	p=.001
	Young	59	524.41		
Right Insula Lobe	Old	59	1041.90	656	p=.006
	Young	59	976.50		
Left Posterior Cingulate Cortex	Old	59	1053.44	655	p=.006
	Young	59	1011.09		
Right Posterior Cingulate Cortex	Old	59	1088.14	623	p=.023
	Young	59	1046.32		
Left Middle Cingulate Cortex	Old	59	939.24	679	p=.002
	Young	59	960.92		
Right Middle Cingulate Cortex	Old	59	938.861	636	p=.014
	Young	59	916.52		
Left Parahippocampal Gyrus	Old	59	1260.84	633	p=.015
	Young	59	1187.61		
Right Calcarine Gyrus	Old	59	1008.39	602	p=.048
	Young	59	966.01		
Left Middle Occipital Gyrus	Old	59	848.33	651	p=.007
	Young	59	797.87		
Left Fusiform Gyrus	Old	59	976.09	612	p=.034
	Young	59	920.68		
Right Fusiform Gyrus	Old	59	1038.32	621	p=.024
	Young	59	987.68		
Left Postcentral Gyrus	Old	59	792.20	711	p=.000
	Young	59	714.99		

Table 5.5. Average T₁ values measured in WM Regions in Cortex Cont.

ROI	Age Group	df	T ₁ (ms) (Median)	Test Statistics (U)	Sig.
Right Postcentral Gyrus	Old	59	799.82	703	p=.001
	Young	59	693.86		
Left Superior Parietal Lobule	Old	59	747.18	671	p=.003
	Young	59	675.84		
Right Superior Parietal Lobule	Old	59	741.43	620	p=.025
	Young	59	689.60		
Left Inferior Parietal Lobule	Old	59	839.48	709	p=.000
	Young	59	775.08		
Right Inferior Parietal Lobule	Old	59	867.977	640	p=.012
	Young	59	794.17		
Left Supramarginal Gyrus	Old	59	912.42	695	p=.001
	Young	59	847.72		
Right Supramarginal Gyrus	Old	59	944.53	687	p=.001
	Young	59	875.95		
Left Angular Gyrus	Old	59	883.67	724	p=.000
	Young	59	800.45		
Right Angular Gyrus	Old	59	918.21	619	p=.026
	Young	59	864.58		
Left Precuneus	Old	59	884.67	721	p=.000
	Young	59	805.33		
Right Precuneus	Old	59	980.58	692	p=.001
	Young	59	918.56		
Left Paracentral Lobule	Old	59	504.00	723	p=.000
	Young	59	414.17		
Right Paracentral Lobule	Old	59	620.34	749	p=.000
	Young	59	516.01		
Left Superior Temporal Gyrus	Old	59	1036.31	631	p=.017
	Young	59	982.72		
Right Superior Temporal Gyrus	Old	59	1089.17	632	p=.016
	Young	59	1029.90		
Left Temporal Pole	Old	59	1062.75	616	p=.029
	Young	59	1011.94		
Right Temporal Pole	Old	59	1059.93	652	p=.007
	Young	59	993.72		

Table 5.5. Average T_1 values measured in WM Regions in Cortex Cont.

ROI	Age Group	df	T_1 (ms) (Median)	Test Statistics (U)	Sig.
Left Middle Temporal Gyrus	Old	59	986.11	664	p=.004
	Young	59	920.99		
Left Medial Temporal Pole	Old	59	938.17	669	p=.003
	Young	59	810.05		
Right Medial Temporal Pole	Old	59	915.09	701	p=.001
	Young	59	784.08		
Left Inferior Temporal Gyrus	Old	59	907.21	626	p=.020
	Young	59	832.84		

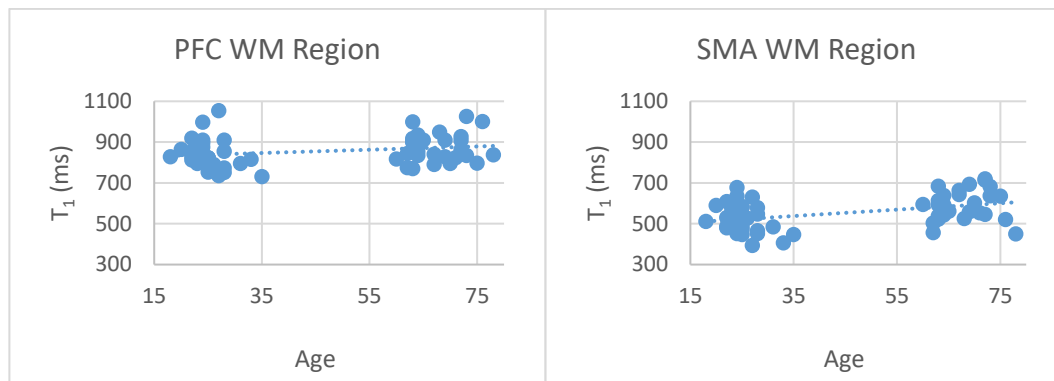


Figure 5.6. The T_1 values of timing structures measured in WM regions of cortex were plotted against age. (PFC: Prefrontal Cortex, SMA: Supplementary motor area).

GM Regions in Cortex: As indicated by Kolmogorov-Smirnov test, T_1 values measured in GM regions of the cortex violated normality assumption ($p \leq .05$). According to a Mann-Whitney U test indicated age-related significant increase in average T_1 values measured in bilateral Pre-central Gyrus, Middle Frontal Gyrus and Inferior Frontal Gyrus (See Table 5.6). The T_1 values of timing structures measured in GM regions of cortex were plotted against age and depicted in Figure 5.7.

Table 5.6. Average T_1 values measured in GM Regions in Cortex

ROI	Age Group	df	T_1 (ms) (Median)	Test Statistics (U)	p
Left Precentral Gyrus	Old	59	834.52	713	p=.000
	Young	59	753.16		
Right Precentral Gyrus	Old	59	865.63	659	p=.005
	Young	59	773.46		
Left Middle Frontal Gyrus	Old	59	856.49	603	p=.047
	Young	59	806.48		
Right Middle Frontal Gyrus	Old	59	812.99	631	p=.017
	Young	59	765.50		
Left Inferior Frontal Gyrus Pars Triangularis	Old	59	1059.50	654	p=.006
	Young	59	1005.36		
Right Inferior Frontal Gyrus Pars Triangularis	Old	59	1030.76	672	p=.003
	Young	59	951.74		
Left Inferior Frontal Gyrus Pars Opercularis	Old	59	1170.35	673	p=.003
	Young	59	1115.11		
Right Inferior Frontal Gyrus Pars Opercularis	Old	59	1094.51	640	p=.012
	Young	59	1032.70		
Left Rolandic Operculum	Old	59	1341.74	631	p=.017
	Young	59	1272.34		
Right Rolandic Operculum	Old	59	1241.11	621	p=.024
	Young	59	1187.69		
Left Supplementary Motor area (SMA)	Old	59	669.46	649	p=.008
	Young	59	597.91		
Right Supplementary Motor area (SMA)	Old	59	687.07	666	p=.004
	Young	59	585.48		
Left Olfactory Cortex	Old	59	1547.76	604	p=.045
	Young	59	1468.75		
Right Olfactory Cortex	Old	59	1505.84	622	p=.024
	Young	59	1454.11		
Right Posterior Cingulate Cortex	Old	59	1487.06	617	p=.028
	Young	59	1456.95		
Left Middle Cingulate Cortex	Old	59	1237.77	616	p=.029
	Young	59	1187.56		
Right Middle Cingulate Cortex	Old	59	1230.24	601	p=.050
	Young	59	1182.23		
Left Parahippocampal Gyrus	Old	59	1465.00	625	p=.021
	Young	59	1386.11		

Table 5.6. Average T_1 values measured in GM Regions in Cortex Cont.

ROI	Age Group	df	T_1 (ms) (Median)	Test Statistics (U)	p
Right Parahippocampal Gyrus	Old	59	1513.61	659	p=.005
	Young	59	1399.44		
Left Middle Occipital Gyrus	Old	59	1041.33	636	p=.014
	Young	59	993.45		
Left Postcentral Gyrus	Old	59	934.36	759	p=.000
	Young	59	828.43		
Right Postcentral Gyrus	Old	59	933.05	686	p=.001
	Young	59	836.42		
Left Superior Parietal Lobule	Old	59	866.11	701	p=.001
	Young	59	791.56		
Right Superior Parietal Lobule	Old	59	878.80	637	p=.013
	Young	59	798.20		
Left Inferior Parietal Lobule	Old	59	1024.82	760	p=.000
	Young	59	943.60		
Right Inferior Parietal Lobule	Old	59	1061.56	691	p=.001
	Young	59	971.33		
Left Supramarginal Gyrus	Old	59	1124.47	732	p=.000
	Young	59	1047.60		
Right Supramarginal Gyrus	Old	59	1186.87	741	p=.000
	Young	59	1108.74		
Left Angular Gyrus	Old	59	1093.86	696	p=.001
	Young	59	998.62		
Right Angular Gyrus	Old	59	1105.87	692	p=.001
	Young	59	1042.93		
Left Precuneus	Old	59	1114.49	664	p=.004
	Young	59	1047.75		
Right Precuneus	Old	59	1225.12	668	p=.003
	Young	59	1133.91		
Left Paracentral Lobule	Old	59	496.39	728	p=.000
	Young	59	496.39		
Right Paracentral Lobule	Old	59	716.47	702	p=.001
	Young	59	619.83		
Left Heschl's Gyrus	Old	59	1462.40	643	p=.010
	Young	59	1390.42		
Right Heschl's Gyrus	Old	59	1437.34	703	p=.001
	Young	59	1383.26		

<i>Table 5.6. Average T₁ values measured in GM Regions in Cortex Cont.</i>							
ROI	Age Group	df	T ₁ (ms) (Median)	Test Statistics (U)	p		
Left Superior Temporal Gyrus	Old	59	1308.18	653	p=.007		
	Young	59	1239.47				
Right Superior Temporal Gyrus	Old	59	1288.60	734	p=.000		
	Young	59	1222.13				
Left Temporal Pole	Old	59	1293.74	611	p=.035		
	Young	59	1210.70				
Right Temporal Pole	Old	59	1251.71	657	p=.006		
	Young	59	1184.69				
Left Middle Temporal Gyrus	Old	59	1201.71	606	p=.042		
	Young	59	1158.85				
Right Middle Temporal Gyrus	Old	59	1240.62	664	p=.004		
	Young	59	1174.58				
Left Medial Temporal Pole	Old	59	1032.43	681	p=.002		
	Young	59	894.93				
Right Medial Temporal Pole	Old	59	1031.15	709	p=.000		
	Young	59	896.38				

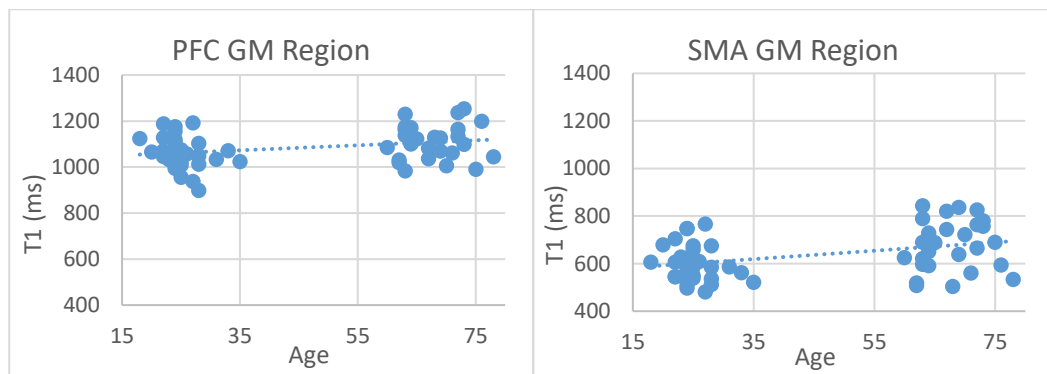


Figure 5.7. The T₁ values of timing structures measured in GM regions of cortex were plotted against age. (PFC: Prefrontal Cortex, SMA: Supplementary motor area).

5.2.2. Signal Measurements in Whole Brain

In subcortical area: A Kolmogorov-Smirnov test indicated that T_1 values in this region had a normal distribution ($p \geq .05$). Independent Samples t-test demonstrated that average T_1 value in bilateral hippocampus, caudate and in thalamus of old group were significantly higher than of younger counterparts, for detailed information see Table 5.2.

WM Regions in Cerebellum: Since Kolmogorov-Smirnov test demonstrated that T_1 in this area did not have a normal distribution ($p \leq .05$), a Mann-Whitney U Test was conducted to compare average T_1 values in WM ROIs measured in Cerebellum across two age groups. The average T_1 value measured in left Cerebellum IX, bilateral Cerebellum X and Cerebellar Vermis u 4 5 of the old participants were significantly higher than in of young participants (see Table 5.3).

GM Regions in Cerebellum: The non-normal distribution of the T_1 values in this region is observed with Kolmogorov-Smirnov test ($p \leq .05$). An Independent-Samples Mann-Whitney U test indicated significant age-related differences in average T_1 measurements in 9 GM regions of Cerebellum. The average T_1 values of old participants measured in bilateral Cerebellum III, cerebellum IV V, Cerebellum X, Cerebellar Vermis u 4 5 and Cerebellar Vermis u 9 were significantly greater than of younger ones (for detail, see Table 5.4).

WM Regions in Cortex: According to Kolmogorov-Smirnov test, T_1 values in these regions of the cortex had a non-normal distribution ($p \leq .05$). A Mann-Whitney U test showed significantly greater average T_1 values of old group measured in bilateral Precentral Gyrus, right Superior Frontal Gyrus, right Middle Frontal Gyrus, right Inferior Frontal Gyrus Pars Triangularis, bilateral Inferior Frontal Gyrus Pars Opercularis, bilateral Rolandic Operculum, bilateral Supplementary Motor area (SMA), right Insula Lobe, bilateral Posterior Cingulate Cortex, bilateral Middle Cingulate Cortex, left Parahippocampal Gyrus, right Calcarine Gyrus, left Middle Occipital Gyrus, bilateral Fusiform Gyrus, bilateral Postcentral Gyrus, bilateral

Superior Parietal Lobule, bilateral Inferior Parietal Lobule, bilateral Supramarginal Gyrus, bilateral Angular Gyrus, bilateral Precuneus, bilateral Paracentral Lobule, bilateral Superior Temporal Gyrus, right Superior Temporal Gyrus, bilateral Temporal Pole, left Middle Temporal Gyrus, bilateral Medial Temporal Pole and left Inferior Temporal Gyrus than of younger group (detailed information in Table 5.5).

GM Regions in Cortex: A Kolmogorov-Smirnov test demonstrated that T_1 values in this area violated the normality assumption ($p \leq .05$) which leads us to nonparametric tests. According to a Mann-Whitney U test indicated age-related significant increase in average T_1 values measured in bilateral Precentral Gyrus, bilateral Middle Frontal Gyrus, bilateral Inferior Frontal Gyrus Pars Triangularis, bilateral Inferior Frontal Gyrus Pars Opercularis, bilateral Rolandic Operculum, bilateral Supplementary Motor area (SMA), bilateral Olfactory Cortex, right Posterior Cingulate Cortex, bilateral Middle Cingulate Cortex, bilateral Parahippocampal Gyrus, left Middle Occipital Gyrus, bilateral Postcentral Gyrus bilateral Superior Parietal Lobule, bilateral Inferior Parietal Lobule, bilateral Supramarginal Gyrus, bilateral Angular Gyrus, bilateral Precuneus, bilateral Paracentral Lobule, bilateral Heschl's Gyrus, bilateral Superior Temporal Gyrus, bilateral Temporal Pole, bilateral Middle Temporal Gyrus and bilateral Medial Temporal Pole (See Table 5.6).

All in all, we have demonstrated that average T_1 values measured in both timing related structures and also whole brain significantly prolonged with increasing age, so that our second hypothesis was verified.

5.2.3. Shuffling of the Subjects Across Age Groups

The subjects were shuffled randomly four times across age groups and the variability of the T_1 values measured in subcortical, cerebellum and cortical area were analyzed. It was observed that none of the structures showed significant differences between two groups produced randomly ($p \geq .05$) although it was demonstrated that there were age-related increases in numerous brain structures in the original grouping.

5.3. Factor Analysis

5.3.1. Subcortical Area

A principal component analysis (PCA) was conducted on 12 T₁ values measured on subcortical area with oblique rotation method (direct oblimin). The sampling adequacy was verified with the Kaiser-Meyer-Olkin measure, KMO=.775. According to Bartlett's test of sphericity $\chi^2(55) = 743.906, p \leq .001$, correlations between variables were sufficiently large for PCA. The eigenvalues of each component were obtained with an initial analysis. Two components had eigenvalues over than Kaiser's criterion of 1 and they jointly explained 78.79% of the variance. Table 5.7 demonstrates the factor loadings after rotation. Bilateral putamen, bilateral globus pallidum, left amygdala and left hippocampus constituted component 1. The second component includes bilateral thalamus, bilateral caudate and right hippocampus. Factor loadings smaller than absolute .50 were suppressed to prevent cross loadings of variables more than one component. Due to cross loading, measurement at right amygdala was excluded from the analysis.

Table 5.7. Summary of exploratory factor analysis results of the Subcortical area (N=60)

ROI	Component	
	Subcortical 1	Subcortical 2
Putamen L	1,038	-,176
Pallidum R	,918	-,018
Putamen R	,876	,094
Pallidum L	,870	,064
Amygdala L	,809	,070
Hippocampus L	,563	,369
Thalamus R	-,083	,964
Thalamus L	-,060	,963
Caudate L	,083	,786
Caudate R	,109	,750
Hippocampus R	,453	,516
Eigenvalues	7.23	1.435
% of variance	65.75	13.04

Note: Factor loadings over .50 appear in bold. R: right, L: left.

5.3.2. Gray Matter Regions in Cerebellum

A principal component analysis (PCA) was conducted on 25 T₁ values measured on Gray Matter (GM) regions on Cerebellum with oblique rotation method (direct oblimin). The Kaiser-Meyer-Olkin measure showed that the sample size is adequate for this analysis, KMO=.826. It was verified that correlations between variables were sufficiently large for PCA according to Bartlett's test of sphericity $\chi^2(300) = 2526.117$, $p \leq .001$. An initial analysis was conducted to acquire the eigenvalues of each component. Five components had eigenvalues over than Kaiser's criterion of 1 and they jointly explained 89.53 % of the variance. Factor loadings smaller than absolute .50 were suppressed to prevent cross loadings of variables more than one component. Table 5.8 demonstrates the factor loadings after rotation. 1 old participant was excluded from Cerebellum analyses due to absence of Cerebellum region in MR image FOV.

Table 5.8. Summary of exploratory factor analysis results of the Cerebellum GM area (N=59)

ROI	Component				
	1	2	3	4	5
Cerebellar Vermis u 8	1,032	,093	,073	,097	,022
Cerebellum Crus1 R	,908	-,132	-,095	,028	,329
Cerebellar Vermis u 7	,869	-,009	-,076	,111	-,165
Cerebellum Crus1 L	,826	-,043	,065	-,201	-,185
Cerebellar Vermis u 9	,670	-,065	-,174	-,201	-,127
Cerebellum VI R	,663	,016	-,281	-,147	-,157
Cerebellar Vermis u 6	,615	,078	-,316	,046	-,339
Cerebellum VI L	,597	-,293	-,053	-,327	-,193
Cerebellum Crus2 L	,117	,944	-,035	-,102	,003
Cerebellum VIII L	-,083	,921	,004	-,042	,044
Cerebellum VII L	-,136	,855	-,033	-,047	,109
Cerebellum IX L	,018	,854	,109	,094	,143
Cerebellar Vermis u 3	-,015	,176	-,948	-,050	-,071
Cerebellum III L	-,056	-,210	-,938	-,003	,093
Cerebellum III R	,081	-,054	-,818	-,120	-,061
Cerebellar Vermis u 1 2	,179	-,146	-,784	,324	,022
Cerebellar Vermis u 4 5	,131	,266	-,753	-,134	-,167
Cerebellum IV V R	,241	,014	-,534	-,373	-,189
Cerebellum IV V L	,216	-,201	-,519	-,447	-,035

Table 5.8. Summary of exploratory factor analysis results of the Cerebellum GM area (N=59) Cont.

ROI	Component				
	1	2	3	4	5
Cerebellum X L					
Cerebellum X R	-,105	,091	-,262	-,811	,133
Cerebellum Crus2 R	,083	,098	,035	-,175	,904
Cerebellum VII R	-,063	,062	,038	-,040	,902
Cerebellum VIII R	-,087	,145	-,005	-,009	,863
Cerebellum IX R	-,040	,486	,030	,152	,569
Eigenvalues	12.827	4.908	1.791	1.549	1.307
% of variance	51.309	19.632	7.163	6.198	5.229

Note: Factor loadings over .50 appear in bold. R: right, L: left, u: unilateral.

5.3.3. White Matter Regions in Cerebellum

A principal component analysis (PCA) was conducted on 25 T₁ values measured on White Matter (WM) regions on Cerebellum with oblique rotation method (direct oblimin). We have investigated the adequacy of the sampling with the Kaiser-Meyer-Olkin measure and it showed that this sampling was appropriate for PCA, KMO=.732. It was verified that correlations between variables were sufficiently large for PCA according to Bartlett's test of sphericity $\chi^2(210) = 1455.254$, $p \leq .001$. An initial analysis was conducted to acquire the eigenvalues of each component. The eigenvalues of four components were over than Kaiser's criterion of 1 and they together explained 82.914 % of the variance. 1 old participant was excluded from Cerebellum analyses due to absence of Cerebellum region in MR image FOV. Also, left & right cerebellum VI, right cerebellum crus 2 and cerebellar vermis u 6 were excluded from the analyses due to cross loading issues. Factor loadings smaller than absolute .55 were suppressed to prevent cross loadings of variables to more than one component. Table 5.9 demonstrates the factor loadings after rotation.

Table 5.9. Summary of exploratory factor analysis results for the Cerebellum WM area (N=59)

ROI	Component			
	1	2	3	4
Cerebellar Vermis u 1 2	,921	,057	,058	,019
Cerebellar Vermis u 3	,907	,043	-,217	,163
Cerebellum III R	,838	-,116	,013	-,115
Cerebellum III L	,811	,066	,121	-,237
Cerebellum IV V R	,641	-,153	-,236	-,210
Cerebellum IV V L	,597	-,224	-,291	-,131
Cerebellum VII L	,109	,966	,104	,045
Cerebellum VIII L	,174	,963	,149	,012
Cerebellum VIII R	-,122	,939	-,058	-,106
Cerebellum IX L	-,078	,882	-,161	,112
Cerebellum VII R	-,183	,870	-,094	-,033
Cerebellum Crus 2 L	,078	,852	-,177	,005
Cerebellum IX R	-,016	,845	,083	-,081
Cerebellum X L	-,068	,118	-,970	,108
Cerebellum X R	,226	-,015	-,772	-,033
Cerebellar Vermis u 4 5	,355	-,054	-,654	-,156
Cerebellar Vermis u 9	-,060	-,009	-,610	-,527
Cerebellum Crus 1 R	-,118	,118	,069	-,965
Cerebellum Crus 1 L	,208	-,022	,025	-,748
Cerebellar Vermis u 7	,296	-,192	-,072	-,687
Cerebellar Vermis u 8	,251	-,095	-,216	-,645
Eigenvalues	9.143	5.174	1.701	1.393
% of variance	43.540	24.639	8.100	6.636

Note: Factor loadings over .55 appear in bold. R: right, L: left, u: unilateral.

5.3.4. Cortical Area

We measured T1 values at 78 ROI for each GM and WM regions of cortex. According to the Kaiser-Meyer-Olkin measure, the sample size was inadequate for PCA. Therefore, the conduction of exploratory factor analysis on purpose of dimension reduction was not appropriate. Regarding with the prior knowledge of the role of prefrontal cortex in timing (e.g. Danckert et al, 2007; Kagerer et al, 2002), we decided to investigate the regions in prefrontal cortex instead of whole cortex.

Gray Matter Regions in Prefrontal Cortex

A PCA was conducted on 10 T₁ values measured on prefrontal cortex GM area with oblique rotation method (direct oblmin). The Kaiser-Meyer-Olkin measure indicated adequate sample size for this analysis, KMO=.763. Also, Bartlett's test of sphericity showed that factor analysis is useful for this data, $\chi^2(45) = 797.010$, $p \leq .001$. The eigenvalues of each component were calculated and three components satisfying Kaiser's criterion (eigenvalue greater than 1) emerged which explained 87.73 % of the variance. Component 1 is composed of superior and middle frontal structures, component 2 includes right inferior frontal structures and component 3 consists of left inferior frontal structures. Factor loadings smaller than absolute .505 were suppressed to prevent cross loadings of variables more than one component. The factor loadings after rotation are presented in Table 5.10.

Table 5.10. *Summary of exploratory factor analysis results on Prefrontal Cortex GM area (N=59)*

ROI	Component		
	1	2	3
GM Superior Frontal Gyrus L	,955	-,045	,037
GM Superior Frontal Gyrus	,929	,177	-,079
GM Middle Frontal Gyrus L	,831	-,161	,355
GM Middle Frontal Gyrus R	,719	,504	-,119
GM Inferior Frontal Gyrus pars Triangularis R	,066	,941	,024

Table 5.10. Summary of exploratory factor analysis results on Prefrontal Cortex GM area (N=59 Cont.)

ROI	Component		
	1	2	3
GM Inferior Frontal Gyrus pars Orbitalis R			
GM Inferior Frontal Gyrus pars Opercularis R	,208	,854	,016
GM Inferior Frontal Gyrus pars Orbitalis L	-,097	,101	,825
GM Inferior Frontal Gyrus pars Triangularis L	,188	,106	,812
GM Inferior Frontal Gyrus pars Opercularis L	,453	,024	,510
Eigenvalues	6.091	1.606	1.076
% of variance	60.91	16.064	10.758

Note: Factor loadings over .505 appear in bold. R: right, L: left.

White Matter Regions in Prefrontal Cortex

A PCA was conducted on 10 T₁ values measured on prefrontal cortex WM area with oblique rotation method (direct oblimin). The Kaiser-Meyer-Olkin measure indicated adequate sample size for this analysis, KMO=.789. Also, Bartlett's test of sphericity showed that factor analysis is useful for this data, $\chi^2(45) = 787.428$, $p \leq .001$. The eigenvalues of each component were calculated and two components satisfying Kaiser's criterion (eigenvalue greater than 1) emerged which explained 81.84 % of the variance. Component 1 represents superior and middle frontal brain areas and component 2 includes inferior frontal structures. Factor loadings smaller than absolute .50 were suppressed to prevent cross loadings of variables more than one component. The factor loadings after rotation are presented in Table 5.11.

Table 5.11. Summary of exploratory factor analysis results on Prefrontal Cortex WM area (N=59)

ROI	Component	
	1	2
Inferior Frontal Gyrus pars Orbitalis R	1,065	-,239
Inferior Frontal Gyrus pars Triangularis R	,939	-,019
Inferior Frontal Gyrus pars Opercularis R	,826	,143
Inferior Frontal Gyrus pars Orbitalis L	,747	,159
Inferior Frontal Gyrus pars Triangularis L	,653	,284
Inferior Frontal Gyrus pars Opercularis L	,586	,302
Superior Frontal Gyrus L	-,145	1,037
Middle Frontal Gyrus L	,190	,832
Superior Frontal Gyrus	,133	,832
Middle Frontal Gyrus R	,430	,603
Eigenvalues	6.925	1.259
% of variance	69.251	12.591

Note: Factor loadings over .50 appear in bold. R: right, L: left.

5.3.5. Subcortical Timing Structures

We conducted a PCA on T₁ values measured in 8 timing structures in subcortical area based on the prior knowledge (Coull, 2011; Meck, Church, and Olton, 1984) with oblique rotation method (direct oblmin). The Kaiser-Meyer-Olkin measure showed that this sampling was appropriate for PCA, KMO=.738. Bartlett's test of sphericity indicated that the correlations between variables large enough to conduct PCA, $\chi^2(28) = 469.062$, $p \leq .001$. An initial analysis was conducted to acquire the eigenvalues of each component. According to Kaiser's criterion, one component had eigenvalue greater than 1 and it explained 69.698 % of the variance. Table 5.12 demonstrates the factor loadings, since only one component extracted the solution couldn't rotated.

Table 5.12. Summary of exploratory factor analysis results on subcortical timing structures (N=60)

ROI	Component
	1
Putamen R	,923
Pallidum L	,891
Pallidum R	,885
Putamen L	,855
Hippocampus R	,842
Hippocampus L	,819
Caudate R	,743
Caudate L	,694
Eigenvalues	5.576
% of variance	69.698

Note: Factor loadings over .50 appear in bold. R: right, L: left.

5.4. Regression Analysis

5.4.1. Subcortical Area

New variables are computed as follows: the average of the T_1 values measured on related ROIs contributing to a component was calculated and examined in regression analysis. A stepwise multiple regression analysis was conducted to test whether T_1 values measured on subcortical area and age of the subject significantly predict BP, WR and DL. When bisection point was predicted it was found that component 1 was a significant predictor ($\beta=.282$, $p \leq .05$) whereas component 2 ($t=-.885$, ns) and age ($t=.068$, ns) did not enter the model, for details see the following table. This analysis indicated that multiple correlation coefficient was .282 and indicating 7.9 % of the variance of bisection point could be accounted for by component 1 ($F(1,57) = 4.908$, $p \leq .05$). WR and DL cannot be significantly predicted by T_1 values measured on

subcortical area and age. BP was plotted against T₁ values measured in Subcortical component 1 and given in Figure 5.8.

Table 5.13. Summary of multiple regression analysis on subcortical area

	B	SE B	β
Constant	1.253	.289	
Component 1	.001	.000	.282*

Note: * = p ≤ .05. Dependent Variable: BP, Independent variable: Component 1.

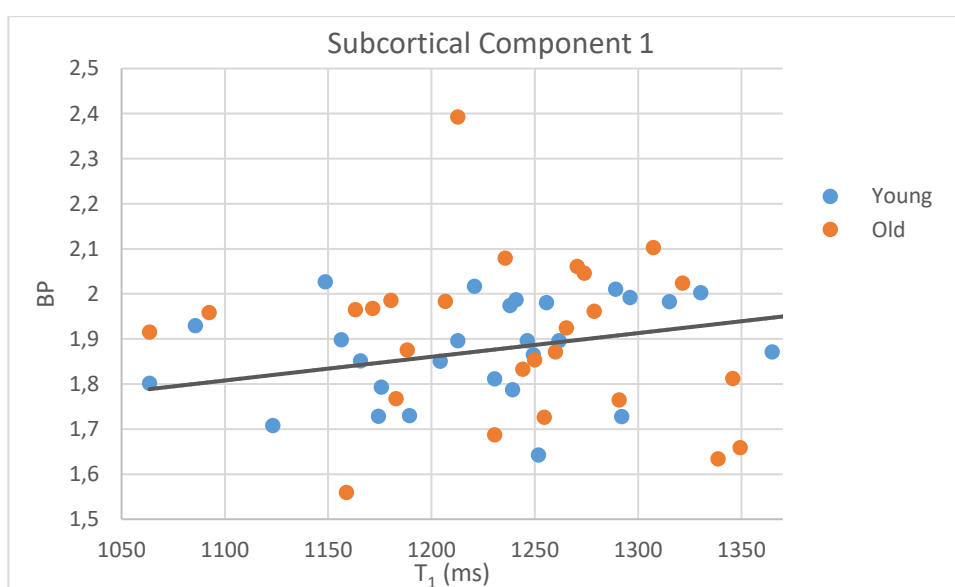


Figure 5.8. BP was plotted against T₁ values measured in Subcortical Component 1.

5.4.2. Gray Matter Regions in Cerebellum

To investigate if the age of the subject and T₁ values measured on cerebellum GM area significantly predict BP, WR and DL a stepwise multiple regression analysis was conducted. In BP prediction, Component 4 (bilateral Cerebellum X) entered to the regression equation and was significantly related to BP, $F(1,57) = 14.310$, $p \leq .01$ while component 1 ($t = -.813$, ns), component 2 ($t = -.676$, ns), component 3 ($t = -.919$, ns), component 5 ($t = .106$, ns) and age ($t = -1.478$, ns) did not enter the model, for details see the following table. The multiple correlation coefficient of the model was .448 and

pointing out that 20.1 % of the variance in BP could be explained by Component 4. WR and DL cannot be significantly predicted by T₁ values measured on cerebellum GM area and age. BP was plotted against T₁ values measured in component 4 and given in Figure 5.9.

Table 5.14. Summary of multiple regression analysis on cerebellum GM area

	B	SE B	β
Constant	1.740	.042	
Component 4	.000	.000	.448**

Note: ** = $p \leq .01$. Dependent Variable: BP, Independent variable: Component 4.

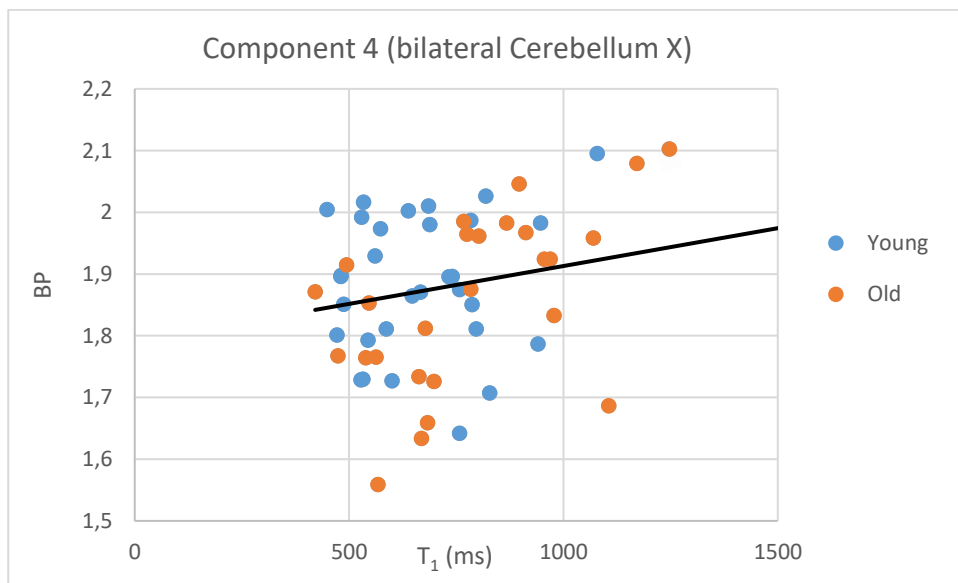


Figure 5.9. BP was plotted against T₁ values measured in component 4.

5.4.3. White Matter Regions in Cerebellum

A stepwise multiple regression was conducted with the aim of testing if T₁ values measured on cerebellum GM area and the age of the subject significantly predict BP, WR and DL. The analysis indicated that Component 3 entered to the regression

equation and was significantly predicted BP, $F(1,57) = 15.824$, $p \leq .01$, for details see the following table. On the other hand, component 1 ($t = -1.291$, ns), component 2 ($t = .164$, ns), component 4 ($t = -1.375$, ns) and age ($t = -1.471$, ns) did not enter the model. Overall, the multiple correlation coefficient of the model was .466 which is an indicator of 20.4 % of the variance in BP could be accounted for component 3. WR and DL cannot be significantly predicted by T_1 values measured on cerebellum WM area and age. BP was plotted against T_1 values measured in component 3 and given in Figure 5.10.

Table 5.15. Summary of multiple regression analysis on cerebellum WM area

	B	SE B	β
Constant	1.532	.090	
Component 3	.000	.000	.466**

Note: **= $p \leq .01$. Dependent Variable: BP, Independent variable: Component 3.

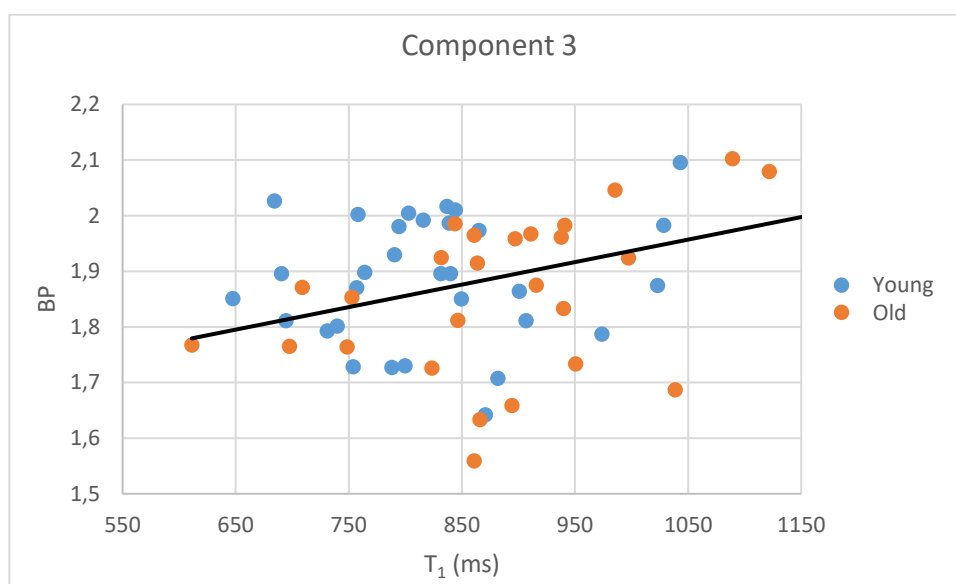


Figure 5.10. BP was plotted against T_1 values measured in component 3.

5.4.4. Prefrontal Cortex

BP, WR and DL could not be predicted by T_1 values measured on prefrontal cortex and age.

5.4.5. Subcortical Timing Structures

To investigate if the age of the subject and the only one component constituted by T_1 values measured on timing structures in subcortical area significantly predict BP, WR and DL a regression analysis was conducted. In BP prediction, this component entered to the regression equation and was significantly related to BP, $F(1,58) = 4.166$, $p \leq .05$. The correlation coefficient of the model was .259 and indicating that 6.7 % of the variance in BP could be explained by subcortical timing structures component. WR and DL cannot be significantly predicted by T_1 values measured on subcortical timing structures and age.

Table 5.16. *Summary of multiple regression analysis on subcortical timing structures*

	B	SE B	β
Constant	1.272	.302	
Component	.000	.000	.259*

Note: * $p \leq .05$. Dependent Variable: BP, Independent variable: Subcortical Timing Component.

CHAPTER 6

DISCUSSION

6.1. Behavioral Experiments

6.1.1. Time Bisection Task

In the current study, we investigated the differences in the time perception between old and young individuals in a time bisection task with a stimulus duration range from 1.25 to 2.5 s. The psychometric functions of the two age groups derived from time bisection task were almost identical, indicating similar timing performances by both young and elderly participants (see Figure 5.1). This visual interpretation was verified by the statistical analysis: the proportion of long responses, $p(\text{long})$, given in each stimulus durations did not differ significantly among age groups. Additionally, there was no shift in the psychometric function curves of young and older individuals that gives information about the location of bisection point (BP). We have demonstrated that BP of the two age groups is not significantly different, in other words, elderly was able to categorize the temporal durations as well as their younger counterparts. This outcome suggested that the accuracy of the timing in bisection task is preserved between 18-78 years in healthy aging. There are ample time bisection studies showing that there is no age-related difference in BP (Lustig & Meck, 2001, 2011; Teresa McCormack, Brown, Maylor, Darby, & Green, 1999; J. H. Wearden et al., 1997).

Although difference in sensitivity to time in older individuals who are 65 years old and over than younger counterparts is reported in terms of impaired sensitivity in various studies (Bisiacchi & Cona, 2016; Buhusi & Meck, 2005; M. Lamotte & Droit-Volet, 2017; Lustig, 2003; Lustig & Meck, 2001; Turgeon, Lustig, & Meck, 2016; J. Wearden, 2016; John H. Wearden, 2012), we did not observe such a difference in WR and DL. Young and older participants demonstrated equal sensitivity to stimulus

durations. Our first hypothesis was that ‘Older population will have less temporal sensitivity in temporal bisection task than younger ones’ but according to first analyses this hypothesis is rejected where we found no significant differences in Weber Ratio between two age population. This might have stemmed from deliberate choice of the stimuli range in our study. Due to the decline in attention capacities of the elderly, age-related differences in time bisection tasks would be more pronounced in long durations than short durations (P. A. Lewis & Miall, 2009).

Another cause of older individuals’ time bisection performance being as good as their younger counterparts could be that older participants might have benefited from the counting strategy during the evaluation of the durations to be judged. We deliberately asked the participants not to count because previously it has been shown that this is the best method to prevent counting (Rattat & Droit-Volet, 2012). Previously, it was showed that counting rate was slower in the older group, perhaps caused by motor slowing or a slowing down of ‘internal tempo’ (S. Vanneste et al., 2001). Counting in a slower pace in older group would brought about longer duration productions, hence reported age-related effects like those obtained by Craik and Hay (1999) may not signify any dramatic change of time perception with increasing age (F. I. M. Craik & Hay, 1999; J. Wearden, 2016). Furthermore, the improvement of temporal discriminations in durations that are longer than 1.6 s by explicit counting was presented (Grondin, Ouellet, & Roussel, 2004). The mentioned improvement is in terms of a decline in variability of timing performances (WR value) (Clément & Droit-Volet, 2006; Grondin et al., 2004). However, since we did not assess a debriefing related to counting state during the experiment, this will remain as a possible explanation.

Previously, it is demonstrated that healthy aged individuals frequently realized their cognitive deficits (Buckley, Norton, Deberard, Welsh-Bohmer, & Tschanz, 2010; Halamish, McGillivray, & Castel, 2011; Varkal et al., 2013). Among other cognitive deficits, being exposed to time distortion is reported to be significantly correlated with temporal performance (Mathilde Lamotte, Izaute, & Droit-Volet, 2012). When the

participants were more aware of their shortcoming, their temporal judgements were reported as more accurate and precise. Moreover, the authors clarified that the older participants used compensatory strategies to cope with their cognitive deficiencies and improve their performance in such a way that more attentional resources were allocated to temporal task. As Scaffolding Theory of Cognitive Aging (STAC) proposed, age-related functional alterations are a part of a cognitive framework which serve as “an attempt to alleviate the cognitive declines associated with aging” (Reuter-Lorenz & Park, 2010, 2014). Hence, we can presume that elderly might have perceived the time bisection task as more difficult than the younger participants and they might have allocated more attentional resources to the temporal judgement. As a result, older adults exhibited a timing performance competing with those of younger adults.

As well as other sensory deficits, age-related visual acuity changes are frequently reported in normal aging (Gates & Mills, 2005; Gittings & Fozard, 1986; Owsley, Sekuler, & Siemsen, 1983). These deficits are closely related with cognitive functioning including attention and memory (Peelle, 2019). Therefore, we examined the visual acuity thresholds of the two age groups with a control experiment. Our findings revealed that both young and older participants could see the visual stimulus optimally and statistical analysis indicated that thresholds of the two age groups did not differ significantly. Hence, it is guaranteed that temporal judgements of the older participants are not confounded with age-linked visual differences.

The preservation of timing ability indicated by our results might be related to the age range of our sample size. In a recent study investigating timing performances in a large cohort of 647 participants, a strong correlation among cognitive functions and both temporal production and discrimination was reported (Bartholomew et al., 2015). The more impressive finding of this study is that timing performance was not related to aging under the control of cognitive scores. The age range of the individuals participated in this study was similar to ours, ranging between 18-67 years. The participants of both our study and Bartholomew et. al’s study are in the “young-old” (under 75 years) category. Previously it was shown that age-related effects on timing

performance may have a late-onset and only become obvious after approximately 75 years of age (Turgeon & Wing, 2012).

6.1.2. Subjective Speed of Passage of Time

Additional to psychometric measurements, we also examined time perception in healthy aging through participants' impressions of time passage. A six-item questionnaire was conducted to assess subjective experience of time passage. In contrast to psychometric measurements, there was a difference in self-rated reports about time perception of the young and old participants. In Item 1 ("How fast does time usually pass for you?") older participants' scores were higher than younger counterparts indicating that elderly reported that time usually passes faster for them than younger ones. This might reveal that older adults are influenced by the phenomenon that "time passes faster as we get older". This finding might be explained by the 'Lower Number of Memorable Events in Older Age' theory which proposes that as people get older they feel that time speeds up because there are fewer memorable events in older age and life evolves to a routine (Fraisse, 1984; James, 1890).

The ratings of Item 2 ("How fast do you expect the next hour to pass?") reveal lower scores for the old participants than the younger ones in that the older participants expect the next hour to pass slower. This might be interpreted as the next hour, which the experiment will be conducted, would be challenging for them and it could be related to their awareness of their own cognitive deficits which has been well-established previously (Buckley et al., 2010; Halamish et al., 2011; Varkal et al., 2013). In the original study that the questionnaire developed (Wittmann & Lehnhoff, 2010), the low correlations between age and Item 1 and Item 2 indicating there is a slight increase in the subjective speed of the passage of time with increasing age.

Our findings contradict with several cross-sectional studies comparing the impressions of recent time passage of the participants from different age groups

(Friedman & Janssen, 2010; S. M. J. Janssen, 2017; S. M. j. Janssen, Naka, & Friedman, 2013; Wittmann, 2005) which report that almost all of the participants indicated a fast passage of time although the difference did not reach statistical significance. The only significant age-related effect was emerged on the 10-year item. A possible reason of this conflict between our results and those in the previous studies may be the difference in sample sizes which is larger for other two studies than ours. Another aspect of this disagreement might be cultural differences peculiar Turkish population in our study and the other studies were conducted in Austria and Germany, New Zealand, and The Netherlands which are similar nations in several aspects.

6.2. MR Analysis

6.2.1. Signal Measurements in Subcortical Area

We have examined age-related changes in T_1 relaxation time in timing structures in subcortical area and independent samples t-test indicated that average T_1 value in bilateral hippocampus and caudate and thalamus of old group were significantly higher than of younger counterparts ($p \leq .05$), (see Table 5.3).

Age-related iron accumulation and demyelination in caudate and hippocampus were reported previously (Daugherty & Raz, 2013; Rodrigue et al., 2013), the dominance of these factors in aging process determines the direction of the T_1 change: iron accumulation shortens T_1 value and increased demyelination prolongs it . Our results suggest possibly lower level of myelin in these structures (Callaghan et al., 2014; Steiger et al., 2016). Similar to our finding, increasing T_1 in caudate was reported in an early study investigating T_1 and T_2 relaxation time estimates in 79 healthy participants (range: 19-85 years) (Agartz, Säaf, Wahlund, & Wetterberg, 1991). We have replicated the outcomes of previous studies reporting T_1 increase in basal ganglia in elderly (Cho et al., 1997; Steen, Gronemeyer, & Taylor, 1995). Significant T_1 prolongation in thalamus and globus pallidus was also observed in a recent study (Okubo et al., 2017).

Our finding is consistent with the recent study examining the effects of aging on T_1 and T_2^* values in a cohort with age range 19 - 75 which reports positive correlation between T_1 in striatum, globus pallidus, periaqueductal grey and age (Keuken et al., 2017). T_1 values reported in this study were higher than ours because data collection was conducted in ultra-high magnetic field (7T). It is well-known that the higher magnetic field strength of the MR system, the higher T_1 values (Rooney et al., 2007b).

Our findings contradict with some recent studies showing an age-related decrease or nonsignificant decline of trend in T_1 in deep GM structures such as caudate, putamen, globus pallidus and nucleus accumbens (Gracien et al., 2017; Okubo et al., 2017). This conflict might be due to coarse measurements within the ROIs in Okubo et. al's study. The ROIs in that study are manually drawn on a single mid-slice on the population-averaged T_1 map. Instead of a single slice and on an averaged image of all subjects, we have created 3D ROIs for each participant. This might have contributed to a better reflection of individual aging patterns. On the other hand, the examination of T_1 changes in deep GM in Gracien et al.'s study was on a combined ROI including caudate nucleus, putamen, globus pallidus and thalamus. The combination of all these structures might have caused loss of region-specific information and complicated the interpretation and generalization of the outcomes. We have masked the subcortical area before ROI creation, in a way that CSF volumes were removed. This is a critical issue especially for the aging brain where atrophy and CSF volume enlargement were prominent. Although Gracien et al.'s study is longitudinal and contributing valuable information to the area, the sample size of 17 subjects limits its generalizability.

6.2.2. Signal Measurements in Whole Brain

Additional to T_1 measurements in the subcortical area, we have created T_1 maps of the whole brain including 218 ROIs defined in the TT_N27 atlas. Comparison of T_1 values between young and old participants showed significant prolongation of T_1 with aging in various structures composed of WM regions in cerebellum (see Table 5.3), GM

regions in cerebellum (see Table 5.4), WM regions in cortex (see Table 5.5) and GM regions in cortex (see Table 5.6).

Our findings of elongated T_1 on WM regions are consistent with the several early works (Callaghan et al., 2014; Cho et al., 1997; Saito et al., 2009; Steen et al., 1995; Suzuki et al., 2006). T_1 value was reported to decrease with aging until a critical age period is reached, then T_1 prolongation started after a point (35.9 years for occipital WM, 41.6 years for frontal and 60.4 years for cortical GM) (Cho et al., 1997). A prolongation of T_1 relaxation time in temporal lobe WM was reported in an early study (Naftali Raz, Millman, & Sarpel, 1990). Similarly, a significant decrease of R_1 ^{*6} in parietal WM with increasing age was shown (B. Draganski et al., 2011). Outcomes from another study proposes that healthy aging is related with substantial T_1 prolongation along the WM surface, it is possibly associated to the alterations in myeloarchitecture and concentrations of myelinated fibers on tissue boundaries (Westlye et al., 2009).

As mentioned above, the T_1 relaxation time alterations during aging have a quadratic pattern; T_1 declines through adolescence and early adulthood, then it reaches to its minimum values in 40-60 years, and finally begins to increase. In cross-sectional studies such as our study it is hard to tell on which region of this quadratic T_1 curve the measured T_1 values fit. Because the quadratic change in T_1 values are rather individual, not the same across all people. The subject specific differences of the aging pattern and their effects on T_1 value might be one of the likely sources of the contradictory outcomes.

Another crucial point worthy of note regards the ROIs used in previous qMRI studies defined either manually or automatically. ROI-based measurements are superior in assessing regional features of the target structures. However, the choice of ROI (e.g. suitability of the ROI to the hypothesis of the study) and inter- and intra-individual differences might influence the effectiveness of the method. Another method used in

⁶ $R_1 = 1/T_1$

qMRI studies is obtaining quantitative measurements with histogram analysis, that shows the data distribution. Histogram-based analyses provide global determination of tissue characteristics with the cost of losing region-specific attributes.

Another potential source of the contradictory results reported in literature may be the usage of different T_1 mapping methods. The most common methods are inversion recovery (IR), Look-Locker (LL) and variable flip angle (VFA). The gold standard of T_1 mapping is postulated as the IR method discovered in 1940s. But, the application of this method is challenging because the acquisition of these maps requires long time (Stikov, Boudreau, et al., 2015). The LL T_1 mapping method is closely related to IR, but this technique is affected by B_1 field inhomogeneity due to the assumption of perfect RF pulses. Contrary to IR and LL techniques, three-dimensional (3D) T_1 maps can be acquired in sustainable durations with VFA (Deoni, Peters, & Rutt, 2005). As mentioned previously, this method requires several spoiled gradient echo (SPGR) images with constant repetition and echo time and different (variable) flip angles. This technique is also haunted by the perfect flip angles assumption. Hence, the calculation of T_1 values based on the exact knowledge of flip angles would introduce a biased outcome, unless a mapping of the B_1 variations is provided. During T_1 estimation, the flip angle of each voxel could be predicted from the slow variation of B_1 pulse amplitude across the FOV. Hence, resulting artifacts in T_1 values accounted for. To overcome this issue a B_1 mapping is crucial, especially at magnetic field strengths that are 3T or higher in which, the variations were reported as higher than lower fields (≤ 1.5 T) (Tofts et al., 2006). Also, the variable flip angle method which we have used in the present study is reported to overestimate T_1 values in vivo due to imperfect spoiling and B_1 bias (Stikov, Boudreau, et al., 2015). To test the robustness of our algorithm under the case of the nominal flip angle is not the actual flip angle, a simulation of flip angle assuming varying $\pm 10\%$ is conducted and the T_1 value of three tissue types measured at corpus callosum, putamen and lateral ventricles for white matter, grey matter and CSF, respectively. The results verified that T_1 values of 3

tissue types in brain are in the range of the T_1 values reported in literature (see Appendix I).

All in all, we have demonstrated that average T_1 values measured in both timing related structures and also whole brain were significantly prolonged with increasing age, so that our second hypothesis was verified.

6.3. Regression Analyses

6.3.1. Relationship Between Subcortical T_1 Characteristics and Time Bisection Task Parameters

Correlation analysis showed significant positive correlations among BP, bilateral hippocampus, amygdala, putamen and pallidum. Factor analyses yielded two components in subcortical area, and regression analysis indicated that component 1 (bilateral putamen, globus pallidus, left amygdala and hippocampus) predicts BP. Here, we demonstrated a significant association between time perception performances and T_1 values. Previously, the relationship between higher T_1 values in hippocampus and poorer cognitive performances such as processing speed and memory was reported in two longitudinal studies, with a large sample size (1.124 volunteers) (Anblagan et al., 2018; Aribisala et al., 2014). The authors stated that microstructural properties measured by qMRI techniques indicate age-related alterations in cellular level which in turn might trigger the change of cognitive functioning before volumetric alterations are detected. Additional to these studies we have proposed a new perspective to the relationship between T_1 relaxation time and cognitive functioning with time perception branch. Similar to T_1 , an association between T_2 relaxation and cognition was reported in such a way that shorter T_2 of WM regions was related to a better cognitive functioning and younger age (Knight et al., 2016).

6.3.2. Relationship Between Cerebellum T₁ and Time Bisection Task Parameters

Correlation and regression analyses revealed the importance of a specific sub-structure of the cerebellum in time bisection: Cerebellum X (according to Larsell's classification). Our findings indicated that T₁ values measured in GM area of bilateral cerebellum X is a significant predictor of the BP. This area also contributed to the prediction of the BP together with WM T₁ of cerebellar vermis u 4 5 and u 9 cerebellum. Cerebellum X is denominated anatomically as "floconodular lobe" and the functional denomination is "vestibocerebellum". The floconodular lobe is unique because it is the only portion of the cerebellum which has a direct input from a sensory nerve (vestibular nerve) (Swenson, 2006).

Previously, it was hypothesized that a dedicated timing machine was located in cerebellum (R. B. Ivry & Keele, 1989; Richard B. Ivry & Schlerf, 2008). However, latter studies reported an association of timing function with some other brain areas such as basal ganglia, inferior parietal cortex and supplementary motor area (Coull et al., 2011). There are detailed neuroimaging (Hove, Fairhurst, Kotz, & Keller, 2013) and neurophysiological (Pressing, Ivry, & Diedrichsen, 2011) studies showing the central role of cerebellum in motor timing tasks. Although the role of cerebellum in motor timing (especially coordinated movements) has been proven, timing functions of cerebellum in perceptual tasks are debatable. After all, there are cerebellar lesion studies reporting an increase in the discrimination thresholds in the most basic temporal tasks (R. B. Ivry & Keele, 1989; Mathiak, Hertrich, Grodd, & Ackermann, 2004; Tregellas et al., 2006).

Previously, the role of cerebellum in time perception with both sub- and supra-second range in a temporal bisection task was investigated via repetitive transcranial magnetic stimulation (rTMS) and results indicated that application of rTMS to the medial or lateral cerebellum caused the participants to produce long responses more often in sub-second range but, cerebellar rTMS did not effect the time bisection performance in supra-seconds (Lee et al., 2007). The outcomes of this study were interpreted as

two different mechanisms in the brain responsible from sub- and supra-second timing. On the other hands, in rodents, the crucial role of lateral cerebellar nucleus (LCN) along with thalamus on the adjustment of the precision on a timing task within supra-second range is demonstrated (Parker et al., 2017). LCN is a part of the deep cerebellar nuclei which have projections to Flocculonodular lobe. Later on, with the accumulating evidence focusing on cerebellum, the interpretation of the role of cerebellum in timing has changed and the contribution of the cerebellum to supra-second timing especially its participation as a regulator is demonstrated (Jahanshahi, Jones, Dirnberger, & Frith, 2006; Mathiak et al., 2004; Ohmae, Kunimatsu, & Tanaka, 2017). A review proposed that the striatum and cerebellum work together with some projections to the cortex (SMA and dorsolateral prefrontal cortex (DLPFC)) and subcortical area (thalamus), and manipulate the precision and continuation of timing processes in both sub- and supra-seconds range (Petter, Lusk, Hesslow, & Meck, 2016). Also in a recent consensus paper, it is stated that the contribution of cerebellum to the supra-second timing through cortical and subcortical circuits should be considered rather than addressing cerebellum as taking role only in sub-second range (Bareš et al., 2018).

Taken together with the literature outcomes, our findings are promising. We have partitioned cerebellum to 50 sub regions and measured T_1 values. The cerebellum X (flocculonodular lobe) stepped forward among all these parts. We believe that this finding is worthy to initiate future studies focusing on this specific area.

The third hypothesis of this study was ‘Behavioral performance of temporal bisection task will be correlated to changes in T_1 relaxation time in both populations.’. Correlation and regression analyses demonstrated that this hypothesis was verified and especially on timing structures.

6.4. Limitations of the Thesis

The present study has several limitations that should be addressed. First of all, the education levels of the young and old participants were significantly different (a lower level of elderly). This might have affected the performances in behavioral experiments. However, we did not observe a decline in the time perception ability of the elderly, so we believe that education level did not interfere with the behavioral results.

Second, our study is cross-sectional which limits the interpretation individual aging patterns. A longitudinal study would provide a better understanding of the age-related changes and minimize the inter-subject variations.

Additionally, individuals participated in our study were basically divided into two age groups, a more uniformly distributed age range might have provided an opportunity to better track the lifelong changes in both time perception and T_1 patterns.

Another limitation regarding to the behavioral experiments is the choice of response recording. The responses of the elderly were recorded by an experimenter while younger participants recorded their own responses. The reason of this choice is explained in method section in detail. Due to this, we are unable to compare the processing speed or the reaction times of the volunteers to overcome this discrepancy.

An important limitation worthy to note in MR analysis is the method of registration. There are two different age groups whose anatomical properties differ a lot. We have created special masks for each participant to remove CSF for a better differentiation of WM and GM. This way, at least we were able to remove the age-dependent increase in ventricles & the effects of atrophy.

One of the most important limitations of this study is due to the method of T_1 mapping. As previously mentioned, the variable flip angle method is vulnerable to B_1 inhomogeneities and hence, flip angle inhomogeneities. The creation of a B_1 map should have been considered and flip angle corrections should have been conducted

to improve the precision and the accuracy of the T_1 estimation. As a preliminary work, we simulated the variability of the flip angles ($\pm 10\%$ change) and showed that T_1 values in our study are still in the range of the values reported in literature. This preliminary work demonstrated the sensitivity of the our T_1 mapping algorithm which produces the T_1 values under the circumstances of the nonhomogeneous flip angles by the degree of 10% change.

6.6. Future Work

Although there are many studies in the literature focusing on time perception and aging, the underlying mechanisms still remains debatable. Gold standards are needed for qMRI methods and temporal experiment designs in this area in which inter-subject variability so high.

Recently, MP2RAGE sequence is developed which produces two images: a whole brain T_1 map and a T_1 -weighted image (Kober et al., 2009). The T_1 maps of MP2RAGE are not affected by above-mentioned inhomogeneities. Validation and reproducibility of the studies using different methods are essential to enlighten inconsistent outcomes in the area.

In the light of several studies conducted by others, we interpreted the outcomes of the time perception experiments via compensatory strategies used by elderly. Both physiological and psychological aspects of the compensation should be investigated in future works.

We have interpreted the age-related alterations observed in T_1 maps in terms of changes in myelination, iron levels and water content of the underlying tissue based on previous works. To unveil the interplay between these parameters in subject specific aging patterns further investigations are warranted.

Addition to T_1 signal variations, volumetric measurements of the brain structures especially taking role in several cognitive functions including time perception should be investigated. The relationship between all these factors should be examined.

The current study has some limitations due to cross-sectional design. The age-related patterns of time perception and the tissue characteristic should be validated also in a longitudinal study so that individual alterations would be assessed in a better way.

This study includes young and health aged participants. A clinical follow-up study comprising of dementia and Alzheimer's disease patients is needed.

CHAPTER 7

CONCLUSION

In this thesis, we have investigated time perception and its relationship with T_1 relaxation time in the region of interests on the whole brain in healthy individuals during aging.

We have demonstrated that the perception of time in the supra-seconds range is preserved with aging when cognitive demands are minimized by reducing task complexity. The temporal perception of the volunteers was investigated with a temporal bisection task of 1.25- and 2.5-seconds range. This task was chosen on purpose to minimize task complexity and hence, cognitive demands. The range of stimuli duration was chosen deliberately because longer durations require additional cognitive functions such as memory and attention which have been indicated as confounding factors in age related differences (M. Lamotte & Droit-Volet, 2017). Additional efforts were made in our study to suppress age-related decline of motor responses observed in elderly. Our findings indicated that there was no difference in discrimination of temporal durations of young and old volunteers, as bisection points of the two cohorts were almost equal. Furthermore, Weber ratio and difference limen that are measures of variability and sensitivity were similar between the age groups. These findings support the compensatory strategies used by elderly and the role of age-related declined cognitive functioning in temporal processing.

To assess the microstructural changes through aging we have used T_1 relaxometry technique which provides tissue specific characteristics. Relaxometry is a suitable tool especially for studies investigating aging. T_1 maps provide a better characterization of the brain tissue and a better basis for the processes such as segmentation of specific brain structures. We have used variable flip angle method for T_1 mapping to enable mapping of tissue characteristics in feasible acquisition times. A T_1 prolongation with increasing age was observed in various brain structures that are important players in both cognitive functions and time perception.

The strength of the current study is in its evaluation of aging patterns in the whole brain with finely adjusted region of interests.

Finally, our analyses to establish a link between time perception and T_1 relaxation showed that there are significant correlations between bisection point and the numerous brain structures including the ones taking role in time perception such as hippocampus, caudate and prefrontal cortex. Additionally, regression analyses revealed that bisection point was significantly predicted by T_1 values in subcortical structures including globus pallidus, putamen and hippocampus, and by a few cerebellar areas. A specific part of the cerebellum attracted attention: T_1 values of bilateral flocculonodular lobe predicted BP by itself among 50 other sub-parts. Our findings suggest that T_1 relaxometry is a promising tool to unveil the underlying mechanisms of cognitive decline and age-related physiological changes.

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CHAPTER 8

APPENDICES

A. SUBJECTIVE PASSAGE OF TIME QUESTIONNAIRE

Bu ölçek farklı zaman dilimlerinde zamanın sizin için geçişine dair bilgi edinmek için sorulan 6 sorudan oluşmaktadır. Uygun cevabı her maddenin yanında ayrılan yere (puanları daire içine alarak) işaretleyin. Cevaplarınızı verirken aşağıdaki puanları kullanın.

[-2]: çok yavaş

[-1]: yavaş

[0]: ne yavaş ne hızlı

[1]: hızlı

[2]: çok hızlı

1. Genellikle zaman sizin için ne kadar hızlı geçer?	-2	-1	0	1	2
2. Sizin için sonraki bir kaç saatin nasıl geçmesini bekliyorsunuz?	-2	-1	0	1	2
3. Geçen hafta ne kadar hızlı geçti?	-2	-1	0	1	2
4. Geçen ay ne kadar hızlı geçti?	-2	-1	0	1	2
5. Geçen yıl ne kadar hızlı geçti?	-2	-1	0	1	2
6. Geçen 10 yıl ne kadar hızlı geçti?	-2	-1	0	1	2

B. MINI MENTAL STATE EXAMINATION (MMSE)

Ad Soyad:
Eğitim (yıl):
T. Puan:

Tarih:
Meslek:

Yaş:
Aktif El:

YÖNELİM (Toplam puan 10)

Hangi yıl içindeyiz..... ()
Hangi mevsimdeyiz ()
Hangi aydayız ()
Bu gün ayın kaçı ()
Hangi gündeysiz ()

Hangi ülkede yaşıyoruz ()
Şu an hangi şehirde bulunmaktasınız ()
Şu an bulunduğunuz semt neresidir ()
Şu an bulunduğunuz bina neresidir ()
Şu an bu binada kaçınıcı kattasınız ()

KAYIT HAFIZASI (Toplam puan 3)

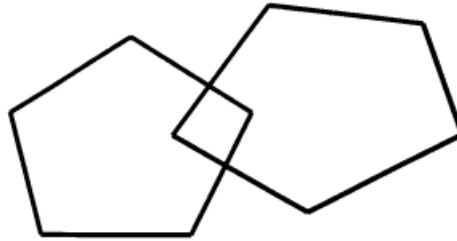
Size birazdan söyleyeceğim üç ismi dikkatlice dinleyip ben bitirdikten sonra tekrarlayın
(Masa, Bayrak, Elbise) (20 sn süre tanınır) Her doğru isim 1 puan ()
DİKKAT ve HESAP YAPMA (Toplam puan 5)
100'den geriye doğru 7 çıkartarak gidin. Dur deyinceye kadar devam edin.
Her doğru işlem 1 puan. (100, 93, 86, 79, 72, 65) ()

HATIRLAMA (Toplam puan 3)

Yukarıda tekrar ettiğiniz kelimeleri hatırlıyor musunuz? Hatırladıklarınızı söyleyin.
(Masa, Bayrak, Elbise)..... ()

LİSAN (Toplam puan 9)

a) Bu gördüğünüz nesnelere isimleri nedir? (saat, kalem) 2 puan (20 sn tut) ()
b) Şimdi size söyleyeceğim cümleyi dikkatle dinleyin ve ben bitirdikten sonra tekrar edin. "Eğer ve fakat istemiyorum" (10 sn tut) 1 puan..... ()
c) Şimdi sizden bir şey yapmanızı isteyeceğim, beni dikkatle dinleyin ve söylediğimi yapın. "Masada duran kağıdı sağ/sol elinizle alın, iki elinizle ikiye katlayın ve yere bırakın lütfen" Toplam puan 3, süre 30 sn, her bir doğru işlem 1 puan..... ()
d) Şimdi size bir cümle vereceğim. Okuyun ve yazıda söylenen şeyi yapın. (1 puan)
"GÖZLERİNİZİ KAPATIN" (arka sayfada)..... ()
e) Şimdi vereceğim kağıda aklınıza gelen anlamlı bir cümleyi yazın (1 puan)..... ()
f) Size göstereceğim şeklin aynısını çizin. (arka sayfada) (1 puan) ()



C. GERIATRIC DEPRESSION SCALE (GDS)

Ad Soyad:

Toplam Puan:

Lütfen yaşamınızın son bir haftasında kendinizi nasıl hissettiğinize ilişkin aşağıdaki sorularda uygun olan yanıtı daire içine alınız.

1) Yaşamınızdan temelde memnun musunuz?

Evet Hayır

2) Kişisel etkinlik ve ilgi alanlarınızın çoğunu halen sürdürüyor musunuz?

Evet Hayır

3) Yaşamınızın bomboş olduğunu hissediyor musunuz?

Evet Hayır

4) Sık sık canınız sıkılır mı?

Evet Hayır

5) Gelecekte umutsuz musunuz?

Evet Hayır

6) Kafanızdan atamadığınız düşünceler nedeniyle rahatsızlık duyduğunuz olur mu?

Evet Hayır

7) Genellikle keyfiniz yerinde midir?

Evet Hayır

8) Başınıza kötü birşey geleceğinden korkuyor musunuz?

Evet Hayır

9) Çoğunlukla kendinizi mutlu hissediyor musunuz?

Evet Hayır

10) Sık sık kendinizi çaresiz hissediyor musunuz?

Evet Hayır

11) Sık sık huzursuz ve yerinde duramayan biri olur musunuz?

Evet Hayır

12) Dışarıya çıkıp yeni birşeyler yaptıktan sonra, evde kalmayı tercih eder misiniz?

Evet Hayır

13) Sıklıkla gelecekte endişe duyuyor musunuz?

Evet Hayır

14) Hafızanızın çoğu kişiden zayıf olduğunu hissediyor musunuz?

Evet Hayır

15) Sizce şu anda yaşıyor olmak çok güzel bir şey midir?

Evet Hayır

16) Kendinizi sıklıkla kederli ve hüzünlü hissediyor musunuz?

Evet Hayır

17) Kendinizi şu andaki halinizle değersiz hissediyor musunuz?

Evet Hayır

18) Geçmişle ilgili olarak çokça üzülüyor musunuz?

Evet Hayır

19) Yaşamı zevk ve heyecan verici buluyor musunuz?

Evet Hayır

20) Yeni projelere başlamak sizin için zor mudur?

Evet Hayır

21) Kendinizi enerji dolu hissediyor musunuz?

Evet Hayır

22) Çözumsuz bir durum içinde bulunduğunuzu düşünüyor musunuz?

Evet Hayır

23) Çoğu kişinin sizden daha iyi durumda olduğunu düşünüyor musunuz?

Evet Hayır

24) Sık sık küçük şeylerden dolayı üzülür müsünüz?

Evet Hayır

25) Sık sık kendinizi ağlayacakmış gibi hissediyor musunuz?

Evet Hayır

26) Dikkatinizi toplamakta güçlük çekiyor musunuz?

Evet Hayır

27) Sabahları güne başlamak hořunuza gidiyor mu?

Evet Hayır

28) Sosyal toplantılara katılmaktan kaçınır mısınız?

Evet Hayır

29) Karar vermek sizin için kolay oluyor mu?

Evet Hayır

30) Zihniniz eskiden olduđu kadar berrak mıdır?

Evet Hayır

D. APPROVAL OF ETHICS COMMITTEE

UYGULAMALI ETİK ARAŞTIRMA MERKEZİ
APPLIED ETHICS RESEARCH CENTER



ORTA DOĞU TEKNİK ÜNİVERSİTESİ
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07 KASIM 2017

Konu: Değerlendirme Sonucu

Gönderen: ODTÜ İnsan Araştırmaları Etik Kurulu (IAEK)

İlgi: İnsan Araştırmaları Etik Kurulu Başvurusu

Sayın Yrd.Doç.Dr. Didem GÖKÇAY ;

Danışmanlığınızı yaptığınız doktora öğrencisi Hayriye AKTAŞ DİNÇER'in "Genç ve Yaşlı katılımcıların süre araştırma deneyi performanslarının karşılaştırılması" başlıklı araştırması İnsan Araştırmaları Etik Kurulu tarafından uygun görülerek gerekli onay 2017-FEN-059 protokol numarası ile 15.11.2017 – 30.05.2018 tarihleri arasında geçerli olmak üzere verilmiştir.

Bilgilerinize saygılarımla sunarım.


Prof. Dr. Ş. Halil TURAN

Başkan V


Prof. Dr. Ayhan SOL

Üye


Prof. Dr. Ayhan Gürbüz DEMİR

Üye

BULUNAMADI
Doç. Dr. Yaşar KONDAKÇI

Üye


Doç. Dr. Zana ÇITAK

Üye


Yrd. Doç. Dr. Pınar KAYGAN

Üye


Yrd. Doç. Dr. Emre SELÇUK

Üye

KLİNİK ARAŞTIRMALAR ETİK KURULU KARAR FORMU

ARAŞTIRMANIN AÇIK ADI	Beynin yaşlanması sürecine ait MR görüntülerinde WM-GM kontrastını iyileştirmek için görüntüleme parametrelerinin optimizasyonu
VARSA ARAŞTIRMANIN PROTOKOL KODU	-

KLİNİK ARAŞTIRMALAR ETİK KURULU	
ETİK KURULUN ÇALIŞMA ESASI	İlaç ve Biyolojik Ürünlerin Klinik Araştırmaları Hakkında Yönetmelik, İyi Klinik Uygulamaları Kılavuzu
BAŞKANIN UNVANI / ADI / SOYADI:	Prof.Dr.Mehmet MELLİ

Unvanı/Adı/Soyadı	Uzmanlık Alanı	Kurumu	Cinsiyet	Araştırma ile ilişkisi	Katılım *	İmza
Prof.Dr.Mehmet MELLİ	Farmakoloji	A.Ü.Tıp Fakültesi	E <input checked="" type="checkbox"/> K <input type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>M. Mellî</i>
Prof.Dr.Irfan SOYKAN	Gastroenteroloji	A.Ü. Tıp Fakültesi	E <input checked="" type="checkbox"/> K <input type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>M. Soykan</i>
Prof.Dr.Serdar ÖZTÜRK	Tıbbi Biyokimya	A.Ü. Tıp Fakültesi	E <input checked="" type="checkbox"/> K <input type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>S. Öztürk</i>
Prof.Dr.Levent YAZICIOĞLU	Kalp ve Damar Cerrahisi	A.Ü. Tıp Fakültesi	E <input checked="" type="checkbox"/> K <input type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>L. Yazıcıoğlu</i>
Prof.Dr.Şule ŞENGÜL	Nefroloji	A.Ü. Tıp Fakültesi	E <input type="checkbox"/> K <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>Ş. Şengül</i>
Prof.Dr.İnci İLHAN	Ruh Sağlığı ve Hastalıkları	A.Ü. Tıp Fakültesi	E <input type="checkbox"/> K <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>İ. İlhan</i>
Prof.Dr.Serap SİVRİ	Çocuk Sağlığı ve Hastalıkları	H.Ü. Tıp Fakültesi	E <input type="checkbox"/> K <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>S. Sivri</i>
Prof.Dr.Zarife ŞENOCAK	Hukuk	A.Ü.Hukuk Fakültesi	E <input type="checkbox"/> K <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	<i>Z. Şenocak</i>
Prof.Dr.Banu ÇAKIR	Halk Sağlığı	H.Ü. Tıp Fakültesi	E <input type="checkbox"/> K <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>B. Çakır</i>
Doç.Dr.Derya GÖKMEN	Biyoistatistik	A.Ü. Tıp Fakültesi	E <input type="checkbox"/> K <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	<i>D. Gökmén</i>
Doç.Dr.Selami Koçak TOPRAK	Hematoloji	A.Ü. Tıp Fakültesi	E <input checked="" type="checkbox"/> K <input type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	<i>S. Koçak</i>
Yrd.Doç.Dr.Nüket KUTLAY	Tıbbi Genetik	A.Ü. Tıp Fakültesi	E <input type="checkbox"/> K <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>N. Kutlay</i>
Yrd.Doç.Dr.Ali Doğan DURSUN	Fizyoloji	A.Ü. Tıp Fakültesi	E <input checked="" type="checkbox"/> K <input type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>A. Doğan</i>
Yrd.Doç.Dr.Önder İLGİLİ	Tıp Tarihi ve Etik	H.Ü.Tıp Fakültesi	E <input checked="" type="checkbox"/> K <input type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input checked="" type="checkbox"/> H <input type="checkbox"/>	<i>O. İlgili</i>
İffet BERKTAŞ	Matematik Mühendisliği	Türkiye Kömür İşletmeleri Genel Müdürlüğü	E <input type="checkbox"/> K <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	E <input type="checkbox"/> H <input checked="" type="checkbox"/>	<i>I. Berktaş</i>

*:Toplantıda Bulunma

Etik Kurul Başkanının
Unvanı/Adı/Soyadı: Prof.Dr.Mehmet Mellî
İmza:

M. Mellî



Not: Etik kurul başkanı, imzasının yer almadığı her sayfaya imza atmalıdır.

E. STUDY ANNOUNCEMENT



ZAMAN ALGISI ÇALIŞMASINA DAVETLİSİNİZ!

İletişim:
METUNeuro Lab
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Çalışma Hakkında

Araştırmamız ODTÜ Enformatik Enstitüsü ve Biyomedikal Mühendisliği ortaklığında yapılmaktadır.

- Bilkent UMRAM'da beyin MR çekimi: 20 dk
- Laptop bilgisayarda deney: 20 dk
- Bilişsel anket: 10 dk

Toplam 50 dk.

Kimler Katılabilir?

- 18-30 ve 65-80 yaş arası
- Herhangi bir nörolojik hastalığı olmayan,
- Vücudunda metal cihazlar bulunmayan (protez, kalp pili, diş çeli)
- Kapalı alan korkusu olmayan gönüllüler.

Hediyelerimiz

- Adınıza **TMA** 'ya fidan bağıışı
- Beyin MR görüntünüzü içeren CD

Gençler! Hem siz gelin hem büyüklerinizi getirin. Sizin adınıza Dr. Ümit Aktaş imzalı bir kitap hediye edelim.

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F. INFORMED CONSENT

ARAŞTIRMAYA GÖNÜLLÜ KATILIM FORMU

Bu çalışma ODTÜ Enformatik Enstitüsü Sağlık Bilişimi öğretim üyelerinden Didem GÖKÇAY tarafından yürütülen ve Biyomedikal Mühendisliği doktora öğrencisi Hayriye AKTAŞ DİNÇER'in 'Yaşlanmanın Zaman Algısı ve Beyindeki T₁ Relaksasyon zamanı üzerine etkileri' isimli doktora tezi kapsamında yapılmaktadır. Bu form sizi araştırma koşulları hakkında bilgilendirmek için hazırlanmıştır.

Çalışmanın Amacı Nedir?

Genç ve yaşlı katılımcıların zaman algısında ve beyin MR görüntülerinden elde edilecek olan T₁ relaksasyon zamanı arasında bir farklılık olup olmadığını değerlendirmektir.

Bize Nasıl Yardımcı Olmanızı İsteyeceğiz?

Araştırma Enformatik Enstitüsü Sağlık Bilişimi bölümü METUNeuro laboratuvarında yapılacaktır. 18-30 yaş arası genç ve 65-80 yaş arası yaşlı yetişkinler katılımcı olarak davet edilecek, katılmak isteyenler yaklaşık 15 dakikalık bir laboratuvar seansına katılacaklardır. Çalışmada sizden bilgisayar ortamında hazırlanmış olan bir test uygulanacaktır ve görüntülerin ekranda gösterildiği süreyi kısa ya da uzun olarak değerlendirmeniz istenecektir. Ayrıca beyin görüntülemesi UMRAM MR Merkezi'nde bulunan ve beyin görüntülemeye yarayan MR cihazı yardımıyla yapılacaktır ve herhangi bir potansiyel risk içermemektedir. MR cihazında bulunduğu üzere, herhangi bir radyoaktif madde ya da X-ışını kullanılmaz, klinik olarak günlük hayatımızda pek çok uygulamaları vardır.

MR çekimi öncesinde katılımcılara toplamda yaklaşık 10 dakika sürecek olan geriatrik depresyon ölçeği, öznel zamanın geçişi anketi ve standardize mini mental test uygulanacaktır. Daha sonra, katılımcılardan yatar pozisyonda başlarına bir aygıt giydirilerek, MR cihazında yatmaları istenmektedir.

MR çekimi, uygun önlemler alındığı takdirde zararsız bir işlemdir. Ancak kapalı yer korkusu olan kişilerin ve vücudunda metal protez, kalp pili, diş teli gibi metal cihazlar bulunan kişiler çalışmaya katılamazlar. MR çekimi başladığında ritmik sesler duyacaksınız. Personel bu sesi azaltmak için size kulak tıkacı temin edecektir. Cihazın içerisinde, iletişim yapabilmeniz için yerleştirilmiş bir ses sistemi bulunmaktadır. Bu vesileyle teknisyen ile konuşmanız mümkündür. Çekim süresince hiçbir kafa hareketi olmaması gerekmektedir. Öksürme, boğazı temizleyecek şekilde yutkunma gibi hareketler çekim kalitesini düşürdüğünden, bazı çekimlerin tekrarlanması gerekebilir. Bu nedenle mümkün olduğunca kafanızı kıpırdatmamanız gerekmektedir. Bu uygulama yaklaşık olarak 20 dakika sürecek olup, kesinlikle size herhangi bir fiziksel zarar vermeyecektir.

Katılımla ilgili bilmeniz gerekenler:

Bu çalışmaya katılmak tamamen gönüllülük esasına dayalıdır. Herhangi bir yaptırıma veya cezaya maruz kalmadan çalışmaya katılmayı reddedebilir veya çalışmayı bırakabilirsiniz. Araştırma esnasında cevap vermek istemediğiniz sorular olursa boş bırakabilirsiniz.

Araştırmaya katılanlardan toplanan veriler tamamen gizli tutulacak, veriler ve kimlik bilgileri herhangi bir şekilde eşleştirilmeyecektir. Katılımcıların isimleri bağımsız bir listede toplanacaktır. Ayrıca toplanan verilere sadece araştırmacılar ulaşabilecektir. Bu araştırmanın sonuçları bilimsel ve profesyonel yayınlarda veya eğitim amaçlı kullanılabilir, fakat katılımcıların kimliği gizli tutulacaktır.

Herhangi bir nöropsikiyatrik hastalığı bulunanların, psikiyatrik ölçekler ve bilişsel testlerin uygulanmasına engel olacak herhangi bir fiziksel engeli (görme, işitme kaybı, motor kayıp vb.) olanların çalışmaya katılması uygun değildir.

Riskler:

Çalışmanın öngörülen herhangi bir riski yoktur.

Bilgilendirilmiş Gönüllü Olur Formu'ndaki tüm açıklamaları okudum. Yukarıda konusu ve amacı belirtilen araştırma ile ilgili tüm yazılı ve sözlü açıklama aşağıda adı belirtilen araştırmacı tarafından yapıldı. Bu çalışmaya tamamen gönüllü olarak katılıyorum ve istediğim zaman gerekçeli veya gerekçesiz olarak yarıda kesip çıkabileceğimi veya kendi isteğime bakılmaksızın araştırmacı tarafından araştırma dışı bırakılabileceğimi biliyorum. Verdiğim bilgilerin bilimsel amaçlı yayınlarda isim bilgilerim olmadan kullanılmasını, görüntü kayıtlarıma sadece araştırmacı veya etik kurul tarafından gizli tutulmak kaydıyla erişilebilmesini kabul ediyorum. Kendi özgür irademle, hiçbir baskı ve zorlama olmadan 'Yaşlanmanın Zaman Algısı ve Beyindeki T₁ Relaksasyon zamanı üzerine etkileri' adlı çalışmaya katılmayı kabul ettiğimi ve bu formun bir kopyasının bana verildiğini aşağıdaki imzamla beyan ederim.

(Formu doldurup imzaladıktan sonra uygulayıcıya geri veriniz).

İsim Soyad

Tarih

İmza

---/---/---

G. T₁ MAPPING MATLAB CODE

```
clear all;
clc;
subjcode='s01.mat';
sinFA_firstimg=sind(3);
TR=20;
TE=4.1500;
FA1=5;
FA2=15;
FA3=30;
% READING ALL SLICES %
N=151; %slice number
im3=load_nii('fa3.nii');
im3=im3.img;
im5=load_nii('fa5.nii');
im5=im5.img;
im15=load_nii('fa15.nii');
im15=im15.img;
im30=load_nii('fa30.nii');
im30=im30.img;
cd('C:\Users\HAYRIYENEUROLAB\Documents\MATLAB\phd_MRs\aktas_nermin');
im3=double(im3);
im5=double(im5);
im15=double(im15);
im30=double(im30);
img_width = 161;
img_height = 191;
final_T1 = zeros(img_width,img_height,N);
```

```

error=zeros(img_width,img_height,N);
error(:,:,:) = 99999999;
tmp_err=zeros(img_width,img_height,N);
tmp2_err=zeros(img_width,img_height,N);
tmp3_err=zeros(img_width,img_height,N);
tmp4_err=zeros(img_width,img_height,N);
t1_start = 200;
t1_end = 4000;
I5 = zeros(img_width,img_height,N);
I15 = zeros(img_width,img_height,N);
I30 = zeros(img_width,img_height,N);
for t1=200:4000;
tmp_err(:,:,)=0;
tmp2_err(:,:,)=0;
tmp3_err(:,:,)=0;
tmp4_err(:,:,)=0;
I5(:,:,:)=(im3(:,:,:)*sind(FA1)/sinFA_firstimg)*(1-exp(-TR/t1))/(1-cosd(FA1)*exp(-
TR/t1));
I15(:,:,:)=(im3(:,:,:)*sind(FA2)/sinFA_firstimg)*(1-exp(-TR/t1))/(1-
cosd(FA2)*exp(-TR/t1));
I30(:,:,:)=(im3(:,:,:)*sind(FA3)/sinFA_firstimg)*(1-exp(-TR/t1))/(1-
cosd(FA3)*exp(-TR/t1));
tmp_err(:,:,) = abs((I5(:,:,:)-im5(:,:,:))) + abs((I15(:,:,:)-im15(:,:,:))) + abs((I30(:,:,:)-
im30(:,:,:)));
tmp2_err(:,:,) = error(:,:,) > tmp_err(:,:,);
error(:,:,) = tmp2_err(:,:,).*tmp_err(:,:,);
tmp3_err(:,:,) = ~tmp2_err(:,:,);
tmp4_err(:,:,) = tmp2_err(:,:,)*t1;
final_T1(:,:,) = (final_T1(:,:,).*tmp3_err(:,:,)) + tmp4_err(:,:,);
end;

```

H. UNIX SCRIPTS

Preprocessing:

% Reading of raw MRI Data

to3d *.IMA

% Deoblique

3dWarp -prefix fa3_deobliqued -deoblique fa3+orig.

3dWarp -prefix fa5_deobliqued -deoblique fa5+orig.

3dWarp -prefix fa15_deobliqued -deoblique fa15+orig.

3dWarp -prefix fa30_deobliqued -deoblique fa30+orig.

3dWarp -prefix mprage_deobliqued -deoblique mprage+orig.

% Registration to Atlas

@auto_tlrc -base TT_N27+tlrc -input fa3_deobliqued+orig.

@auto_tlrc -base TT_N27+tlrc -input fa5_deobliqued+orig.

@auto_tlrc -base TT_N27+tlrc -input fa15_deobliqued+orig.

@auto_tlrc -base TT_N27+tlrc -input fa30_deobliqued+orig.

@auto_tlrc -base TT_N27+tlrc -input mprage_deobliqued+orig.

% Saving as .nii file

3dAFNItoNIFTI -prefix fa3.nii fa3_deobliqued+tlrc.

3dAFNItoNIFTI -prefix fa5.nii fa5_deobliqued+tlrc.

3dAFNItoNIFTI -prefix fa15.nii fa15_deobliqued+tlrc.

3dAFNItoNIFTI -prefix fa30.nii fa30_deobliqued+tlrc.

%Extra Registration for T1

```
@auto_tlrc -xform shift_rotate_scale -maxit 500 -base TT_N27+tlrc. -input  
mprage_deobliqued+orig.
```

%Removal of non-brain parts

```
3dcalc -a 't1+orig.' -expr 'ispositive(a-201)' -prefix skull_mask
```

```
3dcalc -a 'skull_mask+orig.' -b 't1+orig.' -expr 'a*b' -prefix t1_bet
```

```
align_epi_anat.py -dset1 mprage_deobliqued_ns+orig. -dset2 t1_bet+orig. -  
giant_move -deoblique off -align_centers yes -dset2to1 -tlrc_apar  
mprage_deobliqued+tlrc.
```

%Removal of CSF

```
3dcalc -a mprage_deobliqued+tlrc. -expr 'ispositive(a)' -prefix mprage_skull_mask
```

```
3dcalc -a mprage_skull_mask+tlrc. -b t1_bet_tlrc_al+tlrc. -expr 'a*b' -prefix  
t1_mp_bet
```

ROI Creation from Atlas:

```
echo my current directory:
```

```
pwd
```

```
echo ""
```

```
echo the contents of this directory:
```

```
ls
```

```
whereami -mask_atlas_region 'CA_N27_ML:left:precentral_gyrus' -prefix  
precentral_l_mask
```

whereami -mask_atlas_region 'CA_N27_ML:right:precentral_gyrus' -prefix
precentral_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:superior_frontal_gyrus' -prefix
superior_frontal_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:superior_frontal_gyrus' -prefix
superior_frontal_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:superior_orbital_gyrus' -prefix
superior_orbital_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:superior_orbital_gyrus' -prefix
superior_orbital_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:middle_frontal_gyrus' -prefix
middle_frontal_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:middle_frontal_gyrus' -prefix
middle_frontal_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:right:middle_orbital_gyrus' -prefix
middle_orbital_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:middle_orbital_gyrus' -prefix
middle_orbital_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:left:inferior_frontal_gyrus_orbitalis' -
prefix inferior_frontal_gyrus_orbitalis_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:inferior_frontal_gyrus_orbitalis' -
prefix inferior_frontal_gyrus_orbitalis_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:inferior_frontal_gyrus_triangularis'
-prefix inferior_frontal_gyrus_triangularis_l_mask

whereami -mask_atlas_region

'CA_N27_ML:right:inferior_frontal_gyrus_triangularis' -prefix

inferior_frontal_gyrus_triangularis_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:inferior_frontal_gyrus_opercularis'

-prefix inferior_frontal_gyrus_opercularis_l_mask

whereami -mask_atlas_region

'CA_N27_ML:right:inferior_frontal_gyrus_opercularis' -prefix

inferior_frontal_gyrus_opercularis_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:rolandic_operculum' -prefix

rolandic_operculum_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:rolandic_operculum' -prefix

rolandic_operculum_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:sma' -prefix sma_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:sma' -prefix sma_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:olfactory_cortex' -prefix

olfactory_cortex_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:olfactory_cortex' -prefix

olfactory_cortex_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:superior_medial_gyrus' -prefix

superior_medial_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:superior_medial_gyrus' -prefix

superior_medial_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:mid_orbital_gyrus' -prefix

mid_orbital_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:mid_orbital_gyrus' -prefix
mid_orbital_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:rectal_gyrus' -prefix
rectal_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:rectal_gyrus' -prefix
rectal_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:insula_lobe' -prefix
insula_lobe_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:insula_lobe' -prefix
insula_lobe_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:anterior_cingulate_cortex' -prefix
anterior_cingulate_cortex_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:anterior_cingulate_cortex' -prefix
anterior_cingulate_cortex_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:posterior_cingulate_cortex' -prefix
posterior_cingulate_cortex_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:posterior_cingulate_cortex' -
prefix posterior_cingulate_cortex_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:middle_cingulate_cortex' -prefix
middle_cingulate_cortex_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:middle_cingulate_cortex' -prefix
middle_cingulate_cortex_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:hippocampus' -prefix
hippocampus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:hippocampus' -prefix
hippocampus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:parahippocampal_gyrus' -prefix
parahippocampal_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:parahippocampal_gyrus' -prefix
parahippocampal_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:amygdala' -prefix
amygdala_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:amygdala' -prefix
amygdala_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:calcarine_gyrus' -prefix
calcarine_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:calcarine_gyrus' -prefix
calcarine_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cuneus' -prefix cuneus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cuneus' -prefix cuneus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:lingual_gyrus' -prefix
lingual_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:lingual_gyrus' -prefix
lingual_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:superior_occipital_gyrus' -prefix
superior_occipital_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:superior_occipital_gyrus' -prefix
superior_occipital_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:middle_occipital_gyrus' -prefix
middle_occipital_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:middle_occipital_gyrus' -prefix
middle_occipital_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:inferior_occipital_gyrus' -prefix
inferior_occipital_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:inferior_occipital_gyrus' -prefix
inferior_occipital_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:fusiform_gyrus' -prefix
fusiform_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:fusiform_gyrus' -prefix
fusiform_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:postcentral_gyrus' -prefix
postcentral_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:postcentral_gyrus' -prefix
postcentral_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:superior_parietal_lobule' -prefix
superior_parietal_lobule_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:superior_parietal_lobule' -prefix
superior_parietal_lobule_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:inferior_parietal_lobule' -prefix
inferior_parietal_lobule_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:inferior_parietal_lobule' -prefix
inferior_parietal_lobule_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:supramarginal_gyrus' -prefix
supramarginal_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:supramarginal_gyrus' -prefix
supramarginal_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:angular_gyrus' -prefix
angular_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:angular_gyrus' -prefix
angular_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:precuneus' -prefix
precuneus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:precuneus' -prefix
precuneus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:paracentral_lobule' -prefix
paracentral_lobule_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:paracentral_lobule' -prefix
paracentral_lobule_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:caudate_nucleus' -prefix
caudate_nucleus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:caudate_nucleus' -prefix
caudate_nucleus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:putamen' -prefix putamen_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:putamen' -prefix
putamen_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:pallidum' -prefix pallidum_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:pallidum' -prefix
pallidum_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:thalamus' -prefix thalamus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:thalamus' -prefix
thalamus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:heschls_gyrus' -prefix
heschls_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:heschls_gyrus' -prefix
heschls_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:superior_temporal_gyrus' -prefix
superior_temporal_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:superior_temporal_gyrus' -prefix
superior_temporal_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:temporal_pole' -prefix
temporal_pole_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:temporal_pole' -prefix
temporal_pole_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:middle_temporal_gyrus' -prefix
middle_temporal_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:middle_temporal_gyrus' -prefix
middle_temporal_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:medial_temporal_pole' -prefix
medial_temporal_pole_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:medial_temporal_pole' -prefix
medial_temporal_pole_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:inferior_temporal_gyrus' -prefix
inferior_temporal_gyrus_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:inferior_temporal_gyrus' -prefix
inferior_temporal_gyrus_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cerebellum_crus1' -prefix
cerebellum_crus1_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cerebellum_crus1' -prefix
cerebellum_crus1_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cerebellum_crus2' -prefix
cerebellum_crus2_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cerebellum_crus2' -prefix
cerebellum_crus2_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cerebellum_III' -prefix
cerebellum_3_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cerebellum_III' -prefix
cerebellum_3_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cerebellum_IV_V' -prefix
cerebellum_IV_V_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cerebellum_IV_V' -prefix
cerebellum_IV_V_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cerebellum_VI' -prefix
cerebellum_VI_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cerebellum_VI' -prefix
cerebellum_VI_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cerebellum_VII' -prefix
cerebellum_VII_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cerebellum_VII' -prefix
cerebellum_VII_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cerebellum_VIII' -prefix
cerebellum_VIII_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cerebellum_VIII' -prefix
cerebellum_VIII_r_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cerebellum_IX' -prefix
cerebellum_IX_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cerebellum_IX' -prefix
cerebellum_IX_l_mask

whereami -mask_atlas_region 'CA_N27_ML:right:cerebellum_X' -prefix
cerebellum_X_r_mask

whereami -mask_atlas_region 'CA_N27_ML:left:cerebellum_X' -prefix
cerebellum_X_l_mask

whereami -mask_atlas_region 'CA_N27_ML:u:cerebellar_vermis_1_2' -prefix
cerebellar_vermis_u_1_2_mask

whereami -mask_atlas_region 'CA_N27_ML:u:cerebellar_vermis_3' -prefix
cerebellar_vermis_u_3_mask

whereami -mask_atlas_region 'CA_N27_ML:u:cerebellar_vermis_4_5' -prefix
cerebellar_vermis_u_4_5_mask

whereami -mask_atlas_region 'CA_N27_ML:u:cerebellar_vermis_6' -prefix
cerebellar_vermis_u_6_mask

```
whereami -mask_atlas_region 'CA_N27_ML:u:cerebellar_vermis_7' -prefix  
cerebellar_vermis_u_7_mask
```

```
whereami -mask_atlas_region 'CA_N27_ML:u:cerebellar_vermis_8' -prefix  
cerebellar_vermis_u_8_mask
```

```
whereami -mask_atlas_region 'CA_N27_ML:u:cerebellar_vermis_9' -prefix  
cerebellar_vermis_u_9_mask
```

Tissue Type Mask Creation:

```
3dcalc -a t1_mp_bet+tlrc. -b mprage_deobliqued_seg_2.nii.gz -expr 'a*b' -prefix  
t1_mp_bet_wm_masked
```

```
3dcalc -a t1_mp_bet+tlrc. -b mprage_deobliqued_seg_1.nii.gz -expr 'a*b' -prefix  
t1_mp_bet_gm_masked
```

```
3dcalc -a t1_mp_bet+tlrc. -b mprage_deobliqued_seg_0.nii.gz -expr 'a*iszero(b)' -  
prefix t1_mp_bet_csf_removed
```

Subject Specific Masks of Each ROI:

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_crus1_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_crus1_l_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_crus1_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_crus1_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_crus2_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_crus2_l_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_crus2_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_crus2_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_3_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_3_l_sub_gm_mask
```

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_3_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_3_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_IV_V_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_IV_V_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_IV_V_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_IV_V_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_VI_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_VI_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_VI_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_VI_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_VII_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_VII_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_VII_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_VII_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_VIII_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_VIII_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_VIII_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_VIII_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_IX_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_IX_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_IX_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_IX_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_X_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix cerebellum_X_l_sub_gm_mask

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellum_X_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_X_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellar_vermis_u_1_2_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix cerebellar_vermis_u_1_2_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellar_vermis_u_3_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_3_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellar_vermis_u_4_5_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix cerebellar_vermis_u_4_5_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellar_vermis_u_6_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_6_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellar_vermis_u_7_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_7_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellar_vermis_u_8_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_8_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cerebellar_vermis_u_9_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_9_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_crus1_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_crus1_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_crus1_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_crus1_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_crus2_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_crus2_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_crus2_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_crus2_r_sub_wm_mask
```



```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_3_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_3_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_3_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_3_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_IV_V_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_IV_V_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_IV_V_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_IV_V_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_VI_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_VI_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_VI_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_VI_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_VII_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_VII_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_VII_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_VII_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_VIII_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_VIII_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_VIII_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_VIII_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_IX_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_IX_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_IX_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_IX_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_X_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_X_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellum_X_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellum_X_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellar_vermis_u_1_2_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix cerebellar_vermis_u_1_2_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellar_vermis_u_3_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_3_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellar_vermis_u_4_5_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix cerebellar_vermis_u_4_5_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellar_vermis_u_6_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_6_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellar_vermis_u_7_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_7_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellar_vermis_u_8_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_8_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cerebellar_vermis_u_9_mask+tlrc. -expr  
'ispositive(a*b)' -prefix cerebellar_vermis_u_9_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b precentral_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix precentral_l_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b precentral_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix precentral_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_frontal_gyrus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix superior_frontal_gyrus_l_sub_gm_mask
```

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_frontal_gyrus_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix superior_frontal_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_orbital_gyrus_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix superior_orbital_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_orbital_gyrus_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix superior_orbital_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_frontal_gyrus_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix middle_frontal_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_frontal_gyrus_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix middle_frontal_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_orbital_gyrus_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix middle_orbital_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_orbital_gyrus_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix middle_orbital_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_frontal_gyrus_orbitalis_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix inferior_frontal_gyrus_orbitalis_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_frontal_gyrus_orbitalis_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix inferior_frontal_gyrus_orbitalis_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_frontal_gyrus_triangularis_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix inferior_frontal_gyrus_triangularis_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_frontal_gyrus_triangularis_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix inferior_frontal_gyrus_triangularis_r_sub_gm_mask

```

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b
inferior_frontal_gyrus_opercularis_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix
inferior_frontal_gyrus_opercularis_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b
inferior_frontal_gyrus_opercularis_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix
inferior_frontal_gyrus_opercularis_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b rolandic_operculum_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix rolandic_operculum_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b rolandic_operculum_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix rolandic_operculum_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b sma_l_mask+tlrc. -expr 'ispositive(a*b)' -
prefix sma_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b sma_r_mask+tlrc. -expr 'ispositive(a*b)' -
prefix sma_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b olfactory_cortex_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix olfactory_cortex_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b olfactory_cortex_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix olfactory_cortex_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_medial_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix superior_medial_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_medial_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_medial_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b mid_orbital_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix mid_orbital_gyrus_l_sub_gm_mask

```

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b mid_orbital_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix mid_orbital_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b rectal_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix rectal_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b rectal_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix rectal_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b insula_lobe_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix insula_lobe_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b insula_lobe_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix insula_lobe_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b anterior_cingulate_cortex_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix anterior_cingulate_cortex_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b anterior_cingulate_cortex_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix anterior_cingulate_cortex_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b posterior_cingulate_cortex_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix posterior_cingulate_cortex_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b posterior_cingulate_cortex_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix posterior_cingulate_cortex_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_cingulate_cortex_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_cingulate_cortex_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_cingulate_cortex_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_cingulate_cortex_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b parahippocampal_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix parahippocampal_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b parahippocampal_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix parahippocampal_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b calcarine_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix calcarine_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b calcarine_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix calcarine_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cuneus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix cuneus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b cuneus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix cuneus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b lingual_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix lingual_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b lingual_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix lingual_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_occipital_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_occipital_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_occipital_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_occipital_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_occipital_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_occipital_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_occipital_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_occipital_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_occipital_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix inferior_occipital_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_occipital_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix inferior_occipital_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b fusiform_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix fusiform_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b fusiform_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix fusiform_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b postcentral_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix postcentral_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b postcentral_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix postcentral_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_parietal_lobule_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_parietal_lobule_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_parietal_lobule_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_parietal_lobule_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_parietal_lobule_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix inferior_parietal_lobule_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_parietal_lobule_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix inferior_parietal_lobule_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b supramarginal_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix supramarginal_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b supramarginal_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix supramarginal_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b angular_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix angular_gyrus_l_sub_gm_mask

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b angular_gyrus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix angular_gyrus_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b precuneus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix precuneus_l_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b precuneus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix precuneus_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b paracentral_lobule_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix paracentral_lobule_l_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b paracentral_lobule_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix paracentral_lobule_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b heschls_gyrus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix heschls_gyrus_l_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b heschls_gyrus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix heschls_gyrus_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_temporal_gyrus_l_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix superior_temporal_gyrus_l_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b superior_temporal_gyrus_r_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix superior_temporal_gyrus_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b temporal_pole_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix temporal_pole_l_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b temporal_pole_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix temporal_pole_r_sub_gm_mask
```

```
3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_temporal_gyrus_l_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix middle_temporal_gyrus_l_sub_gm_mask
```


3dcalc -a t1_mp_bet_gm_masked+tlrc. -b middle_temporal_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_temporal_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b medial_temporal_pole_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix medial_temporal_pole_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b medial_temporal_pole_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix medial_temporal_pole_r_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_temporal_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix inferior_temporal_gyrus_l_sub_gm_mask

3dcalc -a t1_mp_bet_gm_masked+tlrc. -b inferior_temporal_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix inferior_temporal_gyrus_r_sub_gm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b precentral_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix precentral_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b precentral_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix precentral_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_frontal_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_frontal_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_frontal_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_frontal_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_orbital_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_orbital_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_orbital_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_orbital_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_frontal_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix middle_frontal_gyrus_l_sub_wm_mask

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_frontal_gyrus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix middle_frontal_gyrus_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_orbital_gyrus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix middle_orbital_gyrus_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_orbital_gyrus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix middle_orbital_gyrus_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b  
inferior_frontal_gyrus_orbitalis_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix  
inferior_frontal_gyrus_orbitalis_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b  
inferior_frontal_gyrus_orbitalis_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix  
inferior_frontal_gyrus_orbitalis_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b  
inferior_frontal_gyrus_triangularis_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix  
inferior_frontal_gyrus_triangularis_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b  
inferior_frontal_gyrus_triangularis_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix  
inferior_frontal_gyrus_triangularis_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b  
inferior_frontal_gyrus_opercularis_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix  
inferior_frontal_gyrus_opercularis_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b  
inferior_frontal_gyrus_opercularis_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix  
inferior_frontal_gyrus_opercularis_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b rolandic_operculum_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix rolandic_operculum_l_sub_wm_mask
```

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b rolandic_operculum_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix rolandic_operculum_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b sma_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix sma_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b sma_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix sma_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b olfactory_cortex_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix olfactory_cortex_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b olfactory_cortex_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix olfactory_cortex_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_medial_gyrus_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix superior_medial_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_medial_gyrus_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix superior_medial_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b mid_orbital_gyrus_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix mid_orbital_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b mid_orbital_gyrus_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix mid_orbital_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b rectal_gyrus_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix rectal_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b rectal_gyrus_r_mask+tlrc. -expr 'ispositive(a*b)' -prefix rectal_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b insula_lobe_l_mask+tlrc. -expr 'ispositive(a*b)' -prefix insula_lobe_l_sub_wm_mask

```

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b insula_lobe_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix insula_lobe_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b anterior_cingulate_cortex_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix anterior_cingulate_cortex_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b anterior_cingulate_cortex_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix anterior_cingulate_cortex_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b posterior_cingulate_cortex_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix posterior_cingulate_cortex_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b posterior_cingulate_cortex_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix posterior_cingulate_cortex_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_cingulate_cortex_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_cingulate_cortex_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_cingulate_cortex_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_cingulate_cortex_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b parahippocampal_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix parahippocampal_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b parahippocampal_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix parahippocampal_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b calcarine_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix calcarine_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b calcarine_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix calcarine_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cuneus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix cuneus_l_sub_wm_mask

```

```

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b cuneus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix cuneus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b lingual_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix lingual_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b lingual_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix lingual_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_occipital_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_occipital_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_occipital_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_occipital_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_occipital_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_occipital_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_occipital_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_occipital_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b inferior_occipital_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix inferior_occipital_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b inferior_occipital_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix inferior_occipital_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b fusiform_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix fusiform_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b fusiform_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix fusiform_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b postcentral_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix postcentral_l_sub_wm_mask

```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b postcentral_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix postcentral_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_parietal_lobule_l_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix superior_parietal_lobule_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_parietal_lobule_r_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix superior_parietal_lobule_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b inferior_parietal_lobule_l_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix inferior_parietal_lobule_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b inferior_parietal_lobule_r_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix inferior_parietal_lobule_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b supramarginal_gyrus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix supramarginal_gyrus_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b supramarginal_gyrus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix supramarginal_gyrus_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b angular_gyrus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix angular_gyrus_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b angular_gyrus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix angular_gyrus_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b precuneus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix precuneus_l_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b precuneus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix precuneus_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b paracentral_lobule_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix paracentral_lobule_l_sub_wm_mask
```

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b paracentral_lobule_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix paracentral_lobule_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b heschls_gyrus_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix heschls_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b heschls_gyrus_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix heschls_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_temporal_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_temporal_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b superior_temporal_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix superior_temporal_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b temporal_pole_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix temporal_pole_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b temporal_pole_r_mask+tlrc. -expr
'ispositive(a*b)' -prefix temporal_pole_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_temporal_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_temporal_gyrus_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b middle_temporal_gyrus_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix middle_temporal_gyrus_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b medial_temporal_pole_l_mask+tlrc. -expr
'ispositive(a*b)' -prefix medial_temporal_pole_l_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b medial_temporal_pole_r_mask+tlrc. -
expr 'ispositive(a*b)' -prefix medial_temporal_pole_r_sub_wm_mask

3dcalc -a t1_mp_bet_wm_masked+tlrc. -b inferior_temporal_gyrus_l_mask+tlrc. -
expr 'ispositive(a*b)' -prefix inferior_temporal_gyrus_l_sub_wm_mask

```
3dcalc -a t1_mp_bet_wm_masked+tlrc. -b inferior_temporal_gyrus_r_mask+tlrc. -  
expr 'ispositive(a*b)' -prefix inferior_temporal_gyrus_r_sub_wm_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b hippocampus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix hippocampus_l_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b hippocampus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix hippocampus_r_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b amygdala_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix amygdala_l_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b amygdala_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix amygdala_r_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b caudate_nucleus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix caudate_nucleus_l_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b caudate_nucleus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix caudate_nucleus_r_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b putamen_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix putamen_l_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b putamen_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix putamen_r_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b pallidum_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix pallidum_l_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b pallidum_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix pallidum_r_sub_mask
```

```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b thalamus_l_mask+tlrc. -expr  
'ispositive(a*b)' -prefix thalamus_l_sub_mask
```



```
3dcalc -a t1_mp_bet_csf_removed+tlrc. -b thalamus_r_mask+tlrc. -expr  
'ispositive(a*b)' -prefix thalamus_r_sub_mask
```

Calculation of Subcortical ROIs Average T1 values:

```
3dmaskave -q -mask hippocampus_l_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

```
3dmaskave -q -mask hippocampus_r_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

```
3dmaskave -q -mask amygdala_l_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

```
3dmaskave -q -mask amygdala_r_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

```
3dmaskave -q -mask caudate_nucleus_l_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

```
3dmaskave -q -mask caudate_nucleus_r_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

```
3dmaskave -q -mask putamen_l_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

```
3dmaskave -q -mask putamen_r_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

```
3dmaskave -q -mask pallidum_l_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

```
3dmaskave -q -mask pallidum_r_subj_specific_mask+tlrc.  
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls
```

3dmaskave -q -mask thalamus_l_subj_specific_mask+tlrc.
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls

3dmaskave -q -mask thalamus_r_subj_specific_mask+tlrc.
t1_mp_bet_csf_removed+tlrc. >> subcortical_roi_t1_avg.xls

Calculation of Cerebellum ROIs Average T1 values:

3dmaskave -q -mask cerebellum_crus1_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_crus1_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_crus2_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_crus2_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_3_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_3_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_IV_V_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_IV_V_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_VI_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_VI_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_VII_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_VII_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_VIII_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_VIII_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_IX_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_IX_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_X_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_X_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellar_vermis_u_1_2_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellar_vermis_u_3_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellar_vermis_u_4_5_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellar_vermis_u_6_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellar_vermis_u_7_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellar_vermis_u_8_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellar_vermis_u_9_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cerebellum_t1_avg_gm.xls

3dmaskave -q -mask cerebellum_crus1_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_crus1_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_crus2_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_crus2_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_3_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_3_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_IV_V_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_IV_V_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_VI_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_VI_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_VII_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_VII_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_VIII_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_VIII_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_IX_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_IX_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_X_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellum_X_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellar_vermis_u_1_2_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellar_vermis_u_3_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

3dmaskave -q -mask cerebellar_vermis_u_4_5_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls

```
3dmaskave -q -mask cerebellar_vermis_u_6_subj_specific_wm_mask+tlrc.  
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls
```

```
3dmaskave -q -mask cerebellar_vermis_u_7_subj_specific_wm_mask+tlrc.  
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls
```

```
3dmaskave -q -mask cerebellar_vermis_u_8_subj_specific_wm_mask+tlrc.  
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls
```

```
3dmaskave -q -mask cerebellar_vermis_u_9_subj_specific_wm_mask+tlrc.  
t1_mp_bet_wm_masked+tlrc. >> cerebellum_t1_avg_wm.xls
```

Calculation of Cortical ROIs Average T1 values:

echo my current directory:

```
pwd
```

```
"echo ""
```

echo the contents of this directory:

```
ls
```

```
3dmaskave -q -mask precentral_l_subj_specific_gm_mask+tlrc.  
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls
```

```
3dmaskave -q -mask precentral_r_subj_specific_gm_mask+tlrc.  
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls
```

```
3dmaskave -q -mask superior_frontal_gyrus_l_subj_specific_gm_mask+tlrc.  
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls
```

```
3dmaskave -q -mask superior_frontal_gyrus_r_subj_specific_gm_mask+tlrc.  
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls
```

3dmaskave -q -mask superior_orbital_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask superior_orbital_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_frontal_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_frontal_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_orbital_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_orbital_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_orbitalis_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_orbitalis_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_triangularis_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_triangularis_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_opercularis_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_opercularis_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask rolandic_operculum_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask rolandic_operculum_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask sma_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask sma_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask olfactory_cortex_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask olfactory_cortex_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask superior_medial_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask superior_medial_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask mid_orbital_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask mid_orbital_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask rectal_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask rectal_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask insula_lobe_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask insula_lobe_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask anterior_cingulate_cortex_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask anterior_cingulate_cortex_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask posterior_cingulate_cortex_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask posterior_cingulate_cortex_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_cingulate_cortex_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_cingulate_cortex_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask parahippocampal_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask parahippocampal_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask calcarine_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask calcarine_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask cuneus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask cuneus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask lingual_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask lingual_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask superior_occipital_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask superior_occipital_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_occipital_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_occipital_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask inferior_occipital_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask inferior_occipital_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask fusiform_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask fusiform_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask postcentral_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask postcentral_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask superior_parietal_lobule_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask superior_parietal_lobule_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask inferior_parietal_lobule_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask inferior_parietal_lobule_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask supramarginal_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask supramarginal_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask angular_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask angular_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask precuneus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask precuneus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask paracentral_lobule_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask paracentral_lobule_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask heschls_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask heschls_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask superior_temporal_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask superior_temporal_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask temporal_pole_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask temporal_pole_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_temporal_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask middle_temporal_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask medial_temporal_pole_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask medial_temporal_pole_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask inferior_temporal_gyrus_l_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask inferior_temporal_gyrus_r_subj_specific_gm_mask+tlrc.
t1_mp_bet_gm_masked+tlrc. >> cortical_roi_t1_avg_gm.xls

3dmaskave -q -mask precentral_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask precentral_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_frontal_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_frontal_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_orbital_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_orbital_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_frontal_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_frontal_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_orbital_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_orbital_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_orbitalis_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_orbitalis_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_triangularis_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_triangularis_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_opercularis_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask
inferior_frontal_gyrus_opercularis_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask rolandic_operculum_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask rolandic_operculum_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask sma_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask sma_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask olfactory_cortex_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask olfactory_cortex_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_medial_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_medial_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask mid_orbital_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask mid_orbital_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask rectal_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask rectal_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask insula_lobe_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask insula_lobe_r_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask anterior_cingulate_cortex_l_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask anterior_cingulate_cortex_r_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask posterior_cingulate_cortex_l_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask posterior_cingulate_cortex_r_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_cingulate_cortex_l_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_cingulate_cortex_r_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask parahippocampal_gyrus_l_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask parahippocampal_gyrus_r_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask calcarine_gyrus_l_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask calcarine_gyrus_r_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask cuneus_l_subj_specific_wm_mask+tlrc.

t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask cuneus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask lingual_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask lingual_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_occipital_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_occipital_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_occipital_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_occipital_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask inferior_occipital_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask inferior_occipital_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask fusiform_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask fusiform_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask postcentral_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask postcentral_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_parietal_lobule_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_parietal_lobule_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask inferior_parietal_lobule_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask inferior_parietal_lobule_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask supramarginal_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask supramarginal_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask angular_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask angular_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask precuneus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask precuneus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask paracentral_lobule_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask paracentral_lobule_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask heschls_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask heschls_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_temporal_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask superior_temporal_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask temporal_pole_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask temporal_pole_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_temporal_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask middle_temporal_gyrus_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask medial_temporal_pole_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask medial_temporal_pole_r_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

3dmaskave -q -mask inferior_temporal_gyrus_l_subj_specific_wm_mask+tlrc.
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls

```
3dmaskave -q -mask inferior_temporal_gyrus_r_subj_specific_wm_mask+tlrc.  
t1_mp_bet_wm_masked+tlrc. >> cortical_roi_t1_avg_wm.xls
```

I. FLIP ANGLE INHOMOGENEITY SIMULATIONS

The VFA method is vulnerable to errors in B_1 mapping. B_1 inhomogeneity is one of the large factors increasing errors, especially at high magnetic fields (Stikov, 2015). To test the robustness of our algorithm under the case of the nominal flip angle is not the actual flip angle, a simulation of flip angle assuming varying $\pm 10\%$ is conducted and the T_1 value of three tissue types measured at Corpus Callosum, putamen and lateral ventricles for white matter, grey matter and CSF, respectively. The results verified that T_1 values of 3 tissue types in brain are compatible with literature (Table I.1).

Table I.1. Simulation with $\pm 10\%$ flip angle inhomogeneity

Tissue Type	Young	Old
CSF T_1 Range (ms)	2952-3485	3324-3941
WM T_1 Range (ms)	620-818	606-697
GM T_1 Range (ms)	1225-1370	1177-1312

J. CORRELATION ANALYSIS

Bonferoni's Correction for Multiple Comparisons

Since this is an exploratory research, a great number of correlation coefficients were calculated which increases the risk of a type I error (the probability of obtaining by chance a correlation which actually no true relationship exists). We have calculated the adjusted significance level as follows: for the brain structures that were measured bilaterally, the original level of the significance (5%) was divided by 2 and the correlation coefficients whose p-values were smaller than adjusted significance level were reported as significant. Instead of including all brain areas for correction we included only left and right hemispheres of the same brain structure because, T_1 value is contingent upon the underlying cytoarchitecture of the area. Although there are a total of 218 brain areas these are not contributing to the same measurement. Only left and right counterparts reflect the same measurements. The adjusted significance levels of the multiple comparisons were given below of each table.

J.1. Correlation Between average T₁ values measured in Subcortical area and Time Bisection Task

Correlation analysis indicated that there are significant correlations across BP and bilateral Hippocampus, bilateral Amygdala, bilateral Putamen, bilateral Pallidum (For detail, see Table J.1).

Table J.1. Kendall's Tau Correlation Coefficients in subcortical area

		BP	WR	DL
Left Hippocampus	Correlation Coefficient	.244*	.007	.041
	Effect Size	.059	.000	.002
Right Hippocampus	Correlation Coefficient	.196*	.028	.055
	Effect Size	.038	.000	.003
Left Amygdala	Correlation Coefficient	.236*	-.019	.015
	Effect Size	.056	.000	.000
Right Amygdala	Correlation Coefficient	.227*	.049	.077
	Effect Size	.052	.002	.006
Right Pallidum	Correlation Coefficient	.212*	.068	.091
	Effect Size	.045	.005	.008

*. Correlation is significant at the 0.025 level (2-tailed) for bilateral and 0.05 level for the unilateral structures.

**. Correlation is significant at the 0.005 level (2-tailed) for bilateral and 0.01 level for the unilateral structures.

J.2. Correlation Between average T₁ values measured in WM Regions in Cerebellum and Time Bisection Task

Based on the correlation analysis, bisection point is related with T₁ values measured in WM regions of right Cerebellum Crus 2 and right Cerebellum VIII, given in Table J.2.

Table J.2 Kendall's Tau Correlation Coefficients in WM Regions in Cerebellum

		BP
Right Cerebellum Crus 2	Correlation Coefficient	.210*
	Effect Size	.044
Right Cerebellum VIII	Correlation Coefficient	.202*
	Effect Size	.041

*. Correlation is significant at the 0.025 level (2-tailed) for bilateral and 0.05 level for the unilateral structures.

**. Correlation is significant at the 0.005 level (2-tailed) for bilateral and 0.01 level for the unilateral structures.

J.3. Correlation Between average T₁ values measured in GM Regions in Cerebellum and Time Bisection Task

According to the analyses conducted between T₁ values measured in GM regions of Cerebellum and temporal task outcomes, four regions reported in Table J.3 were correlated with these timing measures.

Table J.3. Kendall's Tau Correlation Coefficients in GM Regions in Cerebellum

		BP	WR	DL
Left Cerebellum X	Correlation Coefficient	.230*	.061	.067
	Effect Size	.053	.004	.004
Cerebellar Vermis u 6	Correlation Coefficient	-.013	-.232**	-.220*
	Effect Size	.000	.054	.048
Cerebellar Vermis u 8	Correlation Coefficient	-.050	-.230**	-.222*
	Effect Size	.002	.053	.049

*. Correlation is significant at the 0.025 level (2-tailed) for bilateral and 0.05 level for the unilateral structures.

**. Correlation is significant at the 0.005 level (2-tailed) for bilateral and 0.01 level for the unilateral structures.

J.4. Correlation Between average T₁ values measured in WM Regions in Cortex and Time Bisection Task

Table J.4. Kendall's Tau Correlation Coefficients in WM Regions in Cortex

	BP	WR	DL
Left Superior Orbital Gyrus	.255**	-.056	-.024
Left Middle Orbital Gyrus	.202*	-.062	-.037
Left Inferior Frontal Gyrus (p Orbitalis)	.216*	-.038	-.018
Left Inferior Frontal Gyrus (p Triangularis)	.266**	-.001	.032
Left Rolandic Operculum	.222*	.065	.091
Left Insula Lobe	.273**	-.004	.032
Right Anterior Cingulate Cortex	.267**	.036	.070
Right Middle Cingulate Cortex	.225*	-.038	-.008
Left Parahippocampal Gyrus	.255**	.031	.067
Right Parahippocampal Gyrus	.236*	.008	.032
Left Superior Occipital Gyrus	.257**	-.011	.032
Left Middle Occipital Gyrus	.229*	.047	.086
Left Fusiform Gyrus	.210*	-.064	-.032
Left Angular Gyrus	.209*	.027	.067
Left Superior Temporal Gyrus	.199*	.065	.088
Left Temporal Pole	.206*	-.006	.012
Left Middle Temporal Gyrus	.244*	.059	.100
Left Medial Temporal Pole	.198*	-.019	.004
Right Medial Temporal Pole	.212*	.020	.057
Left Inferior Temporal Gyrus	.209*	.005	.031
Right Inferior Temporal Gyrus	.239*	.013	.050

*. Correlation is significant at the 0.025 level (2-tailed) for bilateral and 0.05 level for the unilateral structures.

** . Correlation is significant at the 0.005 level (2-tailed) for bilateral and 0.01 level for the unilateral structures.

J.5. Correlation Between average T₁ values measured in GM Regions in Cortex and Time Bisection Task

There were small-to-medium size significant correlations between time bisection experiment outcomes and average T₁ values measured in GM regions of cortex that are depicted in Table J.5.

Table J.5 Kendall's Tau Correlation Coefficients in GM Regions in Cortex

	BP	WR	DL
Left Rolandic Operculum	.272**	-.096	-.048
Right Olfactory Cortex	.205*	.046	.070
Right Mid-Orbital Gyrus	.228*	-.018	.014
Left Insula Lobe	.224*	-.093	-.059
Right Anterior Cingulate Cortex	.237*	-.074	-.042
Right Parahippocampal Gyrus	.206*	-.019	.012
Left Cuneus	.238*	-.005	.033
Left Middle Occipital Gyrus	.239*	.019	.066
Left Fusiform Gyrus	.212*	-.050	-.023
Right Fusiform Gyrus	.202*	-.094	-.063
Left Angular Gyrus	.253**	.075	.114
Left Heschl's Gyrus	.305**	.047	.089
Right Heschl's Gyrus	.227*	-.010	.037
Left Middle Temporal Gyrus	.229**	.083	-.025
Left Inferior Temporal Gyrus	.198*	-.001	.027
Right Inferior Temporal Gyrus	.184*	-.029	.005
Right Lingual Gyrus	.056	-.202*	-.190*

*. Correlation is significant at the 0.025 level (2-tailed) for bilateral and 0.05 level for the unilateral structures.

** . Correlation is significant at the 0.005 level (2-tailed) for bilateral and 0.01 level for the unilateral structures.

CURRICULUM VITAE

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PERSONAL

Date & Place of Birth: Kırıkkale, 01.11.1987

Languages: Turkish (Native), English (Fluent), German (Beginner)

E-mail: aktashayriye@gmail.com

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EDUCATION

- | | |
|-------------------|--|
| 2013- 2019 | Ph.D. in Department of Biomedical Engineering,
Middle East Technical University, Ankara, TURKEY
Thesis title: ‘Investigating the Relationship Between Tissue Characteristics and Time Perception in Healthy Aging’ |
| 2009-2013 | M.Sc. in Department of Biomedical Engineering,
Middle East Technical University, Ankara, TURKEY
Thesis title: ‘Investigation of Age Dependent Contrast and T ₁ Differences in MR Images at 3.0 T: A Study on MPRAGE, Spin Echo and FLASH Protocols’ |
| 2005-2009 | B.Sc. in Electrics and Electronics Engineering Department,
Erciyes University, Kayseri, TURKEY |

WORK EXPERIENCE

2011- ongoing

Research and Teaching Assistant
METU NEURO Neuroimaging Laboratory
Middle East Technical University, Ankara, TURKEY

- Manual and automatic ROI based volumetric and signal measurements on structural brain MR images of young and old adult populations.
- Expertise in MR data acquisition in both structural imaging and fMRI experiment.
- MR imaging parameters optimization based on characterization of tissue parameters via using multi-contrast FLASH sequences.
- Expertise in pre- and post-processing of MR images (using MATLAB, AFNI and FSL).
- Behavioral cognitive task designing by utilizing SuperLab.

2010-2011

Research and Teaching Assistant
Electrics and Electronics Engineering Department
Duzce University, Turkey

- In charge of Microprocessors and PLC Laboratory
- Administrative duties (e.g. Bologna Process)

PROJECTS INVOLVED

- BAP-07-02-2017-004-042 National Project, Researcher, ‘Dynamic Functional Networks and Task-Modulation: A Migraine Study’.

LIST OF PUBLICATIONS

Papers:

- Aktas Dincer Hayriyei Gokcay Didem. ‘Time Bisection Ability in Supra-Seconds is Preserved during Healthy Aging’. Turkish Journal of Geriatrics (In Press).

International Conferences:

Dincer Aktas, Hayriye, and Didem Gokcay. "Evaluation of MRIS of the brain with respect to SNR, CNR and GWR in young versus old subjects." Signal Processing and Communications Applications Conference (SIU), 2014 22nd. IEEE, 2014.

Dincer Aktas, Hayriye, and Didem Gokcay. 'An Investigation of Signal Characteristics and T1 Relaxation Time in Brain MR Images of Young versus Old Healthy Adults' Proceedings of the 11th International Joint Conference on Biomedical Engineering Systems and Technologies, (pp. 147-154). 19-21 January 2018, Madeira, Portugal.

Poster Presentations:

- Dincer, Hayriye Aktas, and Didem Gokcay. "GWR Evaluation of MPRAGE and Multi-Spectral FLASH MRIs of the Brain in Young Versus Old Subjects". Mind, Brain & Body Symposium, March 19-20, 2015 in Berlin.
- Dincer Aktas, Hayriye, and Didem Gokcay. 'Time Bisection Ability is Preserved During Healthy Aging in Supra-Seconds'. 6th International Symposium on Brain and Cognitive Science (ISBCS), 28 April 2019, in Istanbul.

Attended Workshops and Meetings

- The Role of Thalamus in Sensory Stimuli Discrimination Workshop. 'Dynamic Functional Network Connectivity and Task-Modulation: An Investigation Focused on Migraine'. March 3, 2017. Gazi University Neuropsychiatry of Education, Research and Application Center
- 20th Turkish Magnetic Resonance Association Annual Meetings, May 21-23, 2015. Ankara.

- ITAP International Summer School and Workshop on Brain Dynamics, Marmaris, 2012.
- 10. National Neuroscience Congress, April 9-12, 2011, İstanbul University.

Assisted Courses

Spring 2019	Reasoning Under Uncertainty
Fall 2018	Biological Foundations of Psychology
Fall 2013	Medical Image Analysis
Spring 2012, 2013	Medical Imaging Techniques
Fall 2012, 2013	Neuroimaging: Anatomy, Physiology and Function of the Human Brain
Spring 2012, 2013	Brain Dynamics and Oscillations
Spring 2012	Advanced Topics in Medical Image Analysis
Spring 2012	High Temporal Resolution Brain Imaging with EEG and MEG
Spring 2011	Microprocessors and PLC

Awards

- July - October 2010 YOK (Council of Higher Education) funding, The European School of English language school in Malta.
- 2008-2009
Academic Year Honour Student in Engineering Faculty, Erciyes University
- 2005-2006
Academic Year Honour Student in Engineering Faculty, Erciyes University

RESEARCH INTERESTS

- Biomedical signal and image processing
- Healthy brain aging
- MR Relaxometry (especially T₁ mapping)
- Segmentation
- MRI parameter adjustment
- Time perception
- Expertise in MR data collection and processing