

CORTICAL THICKNESS IN MAJOR DEPRESSIVE DISORDER

CHANGES IN CORTICAL THICKNESS IN MAJOR DEPRESSIVE DISORDER
ACROSS THE LIFESPAN

By
WANDA TRUONG, BSc

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AUTHOR: Wanda Truong, BSc (Western University)

SUPERVISOR: Geoffrey B.C. Hall, PhD

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Abstract

This thesis presents research investigating structural neural correlates of major depressive disorder (MDD). Although research has shown many clear clinical differences between early- and late-onset MDD, they are still subject to the same diagnostic criteria and treatment strategy. Whether these differences translate into differences in cortical structure was examined in this study. By directly comparing early-onset (EOD) and late-onset (LOD) patients, we test whether age-of-onset results in changes in the extent or spatial pattern of cortical thinning.

Chapter 1 provides a general background on the cerebral cortex, followed with a special focus on cortical thickness. Chapter 2 presents a comprehensive review of the clinical and neurobiological literature on major depressive disorder as it pertains to age-of-onset. Three working hypotheses regarding the differences between early- and late-onset depression are presented and discussed.

The results presented in this thesis show that there are both differences and similarities in cortical thickness between patients with EOD and LOD, with differences reflecting spatial extent, region-specificity, and magnitude of thickness differences. We confirmed the hypothesis of greater thinning in the dorsal lateral prefrontal cortex in depressed patients compared to healthy controls. We also correlated cortical thickness with clinical variables, which resulted in the finding of a positive correlation in the posterior cingulate cortex with illness severity.

Few studies have used age-of-onset as a factor, which may account for some of the heterogeneity and inconsistent results seen in studies of MDD. We found that depression onset in early life is associated with greater disturbances in cortical thickness than LOD, possibly reflecting atypical development. These results provide novel insights into vulnerability and how development of depression is differentially affected by age.

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LIST OF ABBREVIATIONS

ANCOVA/ANOVAAnalysis of variance/Analysis of covariance
ACCAnterior cingulate cortex
BABrodmann area
BDI-IIBeck depression inventory version two
CIVETCorticomeric iterative vertex-based estimation of thickness
CLASPConstrained laplacian anatomic segmentation using proximity
CREBcAMP response element binding protein
CRHR1Corticotropin-releasing hormone type 1 receptor
DLPFCDorsal lateral prefrontal cortex
DSM-IVDiagnostic and statistical manual version four
DMNDefault mode network
ECTElectroconvulsive therapy
EODEarly-onset depression
fMRIFunctional magnetic resonance imaging
FOVField of view
GLMGeneral linear model
HAMDHamilton depression rating scale
HCHealthy control
HPAHypothalamic-pituitary-adrenal
LODLate-onset depression
MDDMajor depressive disorder
MNIMontreal neurological institute
mPFCMedial prefrontal cortex
MRIMagnetic resonance imaging
mRNAMessenger ribonucleic acid
PCCPosterior cingulate cortex
PTSDPost-traumatic stress disorder

SBM	Surface-based morphometry
SCID	Structured Clinical Interview for the DSM-IV
SNAP-25	Synaptosomal associated protein 25
TMS	Transcranial magnetic stimulation
VBM	Voxel-based morphometry
vmPFC	Ventral medial prefrontal cortex
3D SPGR	Three-Dimensional Spoiled Gradient Recalled Acquisition in Steady State
5HTTLPR	Serotonin transporter-linked polymorphic region

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis contains a total of 4 chapters: Chapter 1 and 2 provide a background of cortical thickness and early- and late-onset depression, respectively; Chapter 3 is the manuscript of an empirical journal article; Chapter 4 discusses the results of the work, clinical implications and conclusions. Data collection of structural magnetic resonance imaging (MRI) data took place between 2005- 2012 at St. Joseph's Healthcare Hamilton. Participants were recruited through the Mood Disorder's Program (MDP) and the Women's Health Concerns Clinic (WHCC) to take part in various functional MRI studies. Healthy control participants were also recruited to take part in the same studies.

This study was conceived by Dr. Geoffrey Hall and myself. Data collection was carried out by previous students and research staff and supervised by Drs. Geoffrey Hall, Glenda MacQueen, Claudio Soares, and Benecio Frey. Data management was carried out by students in Dr. Margaret McKinnon's lab and myself. I was responsible for data management and reduction, pre-processing of anatomical MRI data, quality control of cortical thickness data, statistical analysis of structural and demographic data, and manuscript preparation. Drs. Luciano Minuzzi and Emma Duerden assisted in the statistical analysis of cortical thickness data. Portions of this work were presented at the 2012 Society of Biological Psychiatry annual conference in Philadelphia, PA.

The paper presented in Chapter 3 (Changes in cortical thickness across the lifespan in major depressive disorder) will be submitted for review to the journal

Biological Psychiatry, 2012. This paper compares cross-sectional cortical thickness data in patients with major depressive disorder and age-matched, healthy control participants. Patients were grouped and analyzed by age-category as early- or late-onset. This study also uses demographic and clinical data as co-variates.

CHAPTER 1

GENERAL INTRODUCTION

This thesis presents a study on cortical thickness in patients with major depressive disorder (MDD) using archival magnetic resonance imaging (MRI) data and a case-control, cross-sectional design. It uses a theory-driven approach to test the following hypotheses concerning the disease mechanisms underlying age-of-onset in MDD: i) neurotoxicity hypothesis ii) vulnerability hypothesis iii) final common pathway hypothesis. The main aim of this investigation is to determine whether there is a differential effect on cortical thickness in patients who differ in their age-of-onset. There have been numerous studies examining clinical features of early- (EOD) and late-onset depression (LOD), but less is known regarding neurobiological differences.

The pathological disease process of many neuropsychiatric diseases is known to affect the structural integrity of the cerebral cortex, examples include significant reductions in cortical thickness observed in Alzheimer's disease (Singh, Chertkow, Lerch, Evans, Dorr, & Kabani, 2006) and schizophrenia (Van Haren, et al., 2011). Research has shown that the effects of anti-depressants used to treat MDD act on intracellular cascades that promote cellular survival pathways, maintaining the integrity of cellular structures (*i.e.* dendritic branches, size of cell body), and protecting the viability of synapses (Duman, Heninger, & Nestler, 1997; Manji, Drevets & Charney, 2001). These findings have implications for cortical thickness as a mediator of treatment response. This study also extends research findings of cortical thickness differences in the MDD population and the possible role of cortical thickness as an endophenotype

(Peterson, et al., 2009). Finally, a study analyzing cortical gyrification was able to distinguish patients with early-, intermediate-, and late-onset bipolar disorder (Penttila, et al., 2009). By examining changes in cortical thickness across the lifespan of patients with depression, this study contributes to our understanding of the disease mechanisms involved in the etiology of depression.

The following overview consists of two background sections, Chapter 1 provides an overview of the structural and functional organization of the cerebral cortex, and cortical thickness in particular, followed by an exhaustive literature review of cortical thickness studies in the MDD population; Chapter 2 reviews the clinical and neurobiological evidence for differences in patients with early- compared to late-onset depression.

In Chapter 3 an empirical analysis of cortical thickness is presented in the form of a manuscript. It addresses whether the cortex is differentially impacted by age-of-onset by directly comparing patients with an early-onset of MDD and those with a late-onset. Here, we show that there are both differences and similarities in cortical thickness between patients with EOD and LOD, with differences reflecting both spatial extent, region-specificity, and magnitude of thickness differences. We confirmed the hypothesis of greater thinning in the dorsal lateral prefrontal cortex in depressed patients compared to healthy controls, and EOD patients exhibited a larger expanse of thinning than LOD patients. We also correlated cortical thickness with clinical variables, which resulted in the finding of a positive correlation in the posterior cingulate cortex with illness severity.

These results provide the first documentation of neuroanatomical differences between EOD and LOD, and may have implications in the planning of treatment strategies.

Finally, the results of the study are discussed in Chapter 4 within the framework of the three aforementioned hypotheses, followed by conclusions and a discussion on clinical implications. The results of this study corroborate previous studies in the literature and provoke novel insights into the developmental neurobiology of depression. The results of this study has also generated several hypotheses that can be investigated via longitudinal studies.

1.1 Cerebral Cortex

The cerebral cortex—the outermost layer of the brain—is the most phylogenetically recent brain structure to evolve. All brains are composed of the same basic building blocks and operate on similar physiological principles. What, then, makes the human brain capable of its cognitive complexity, not seen in other primates? Cognitive functions that are thought to be unique to humans include language (Rilling, Glasser, Jabdi, Andersson, & Preuss, 2011), creativity (Carruthers, 2002), and mentally representing abstract concepts, such as the ability to understand metaphors (Sapolsky, 2010), all of which can be attributed to the cerebral cortex. Comparatively, humans have the largest cerebral cortex to body mass ratio, and it has been suggested that this is the essential distinguishing feature explaining the exceptional cognitive abilities humans have over animals and other primates (Kandel, Schwartz, & Jessell, 2000). However, a recent critical review has shown that it is not the relative size of the brain that matters, but the absolute number of neurons (Herculano-Houzel, 2009). This increase in the number of neurons is linearly scaled, however, the impact of having more neurons is exponential; With more neurons, which represents greater information-processing capacity, there can be more connections made, both within and between regions (Herculano-Houzel, 2009). Although humans and primates share similar basic neuroanatomy, it has been suggested that humans have harnessed the same neural structures to conduct more complex tasks (Sapolsky, 2010). For example, the insular cortex is activated in humans in response to both the visceral feeling of disgust (e.g. in response to a foul odour) as well as to moral disgust (Borg, Lieberman, & Khiel, 2008).

The highly convoluted surface of the human brain is in stark contrast to non-human primates, whose cortical surfaces are considerably smoother (Zilles, Armstrong, Schleicher & Kretschmann, 1988). The deep sulcation and gyrification patterns of the human cortex are a result of increased surface area, where folding is a “natural outcome of increasing brain size” (Toro, Perron, Pike, Richer, Veillette, Pausova, & Paus, 2008). The folding takes place along a rostral to caudal gradient, resulting in the greatest folding in the prefrontal cortex (Toro, et al., 2008). The cortex develops from the anterior portion of the neural plate. Neurons and glia then migrate from the ventricular zone of the neural plate in an “inside-out” manner, where newly formed neurons migrate to the outside of the cortex to form vertical columns, or radial units (Rakic, 1988). Van Essen (1997) proposed that cortical folding is driven by tension along axons. Rather than expanding surface area, which would take up to 3 times the amount of space in the intracranial cavity, folding decreases volume and tension along parallel axonal fibres.

1.2 Principles of Cortical Organization

By studying the structure of the cortex we can begin to understand normal functioning as well as pathological anatomy. Santiago Ramon y Cajal, using the method of Golgi staining to elucidate the cytoarchitecture of the cortex, has contributed greatly to the advancement of neuroscience; although many of his contemporaries studying histological samples and post-mortem brain slices sought to understand specific pathologies, Ramon y Cajal’s work has unveiled several key fundamental

neurobiological principles of how the nervous system is organized (DeFelipe & Jones, 1988).

1.2.1 *Structural organization*

Principles that govern anatomical organization of the cortex across all species, are as follows (Kandel, et al., 2000):

- i) A variety of neuronal types make up the cortex, broadly classified as projection and interneurons (Ramon y Cajal, 1899).
- ii) Horizontal layers connect functional regions, with the neocortex organized into six distinct layers (von Economo & Koskinas, 1925; Brodmann, 1909). This laminar structure allows for precise organization of inputs and outputs from specific functional regions. For example, layer 4 typically receives and integrates sensory information from the thalamus and is also the thickest layer (Kandel, et al., 2000).
- iii) Within a functional region, neurons are organized into vertical columns, processing a particular stimulus type, as demonstrated by Hubel and Weisel (1962) in the primary visual cortex. Columns are further organized into hypercolumns, such that a functional region, or module, can be understood as a collection of hypercolumns.
- iv) Forty-seven distinct functional regions were first demarcated by Brodmann (1909) based on the subtle changes in cytoarchitecture across the cerebral surface. Later, von Economo and Koskinas (1925) identified 5 additional areas,

and 52 Brodmann areas (BA) are now recognized. Regional specialization of the cortex is a result of tissue differentiation during development mediated by intrinsic programming, inducing factors, and local afferent inputs.

Cytoarchitectonic areas are also functionally unique (Kandel, et al., 2000).

- v) Functional systems in the cortex are hierarchically organized to fulfill higher-order sensorimotor and cognitive processing. For example, visual processing takes place in several distinct areas that work together to form networks (e.g. “what” and “where” streams). Thus, rapid transfer of information between areas are achieved through both serial and parallel processing (Kandel, et al., 2000).

1.2.2 Functional organization

Steven Pinker (1997) and others have argued that evolution has shaped the functions that have evolved in humans and have resulted in cognitive modules “...each with a specialized design that makes it an expert in one area of interaction with the world.” On a macroscopic level, the cortex is divided anatomically by three fissures (longitudinal, central, and Sylvian) that separate it into 4 lobes (prefrontal, temporal, parietal, occipital). Within each lobe, the cortex is further divided into functional modules, separated by sulci and roughly corresponding to Brodmann areas (Kandel, et al., 2000). The structure-function relationship is illustrated by the study of Einstein’s post-mortem brain, whose exceptional cognitive abilities seems to have been reflected in abnormal neuroanatomy (Witelson, Kigar, & Harvey, 1999). The cognitive aspects of mathematical processing are thought to involve both language and visuo-spatial

processing (Dehaene, et al., 1999). Language is thought to subserve the encoding and retrieval of numerical facts (mediated by supralingual gyrus), whereas visuo-spatial processing plays a role in mental manipulation of quantities and magnitudes (mediated by inferior parietal gyrus). Einstein was particularly adept in the latter function and, interestingly, his inferior parietal cortex was 15% larger than controls. In addition, Einstein lacked a Sylvian fissure, which the authors suggested lead to improved communication between neurons in the temporal and parietal areas (Witelson, Kigar, & Harvey, 1999).

Globally, functional regions are organized into networks, allowing for segregation and integration of information processing. We are beginning to understand the brain as a highly organized system of functional networks, with the whole, or network activation, being greater than the sum of its parts (Power, Fair, Schlaggar, & Petersen, 2010). Brain networks have both local and global network properties, are organized hierarchically into hubs or modules, and are characterized by ‘small-world’ properties, that is the principle that they are organized to exhibit maximum efficiency with minimum energy and wiring cost (He, Chen & Evans, 2007).

1.2.3 Neuroplasticity

Neuroplasticity refers to the ability of neurons to change with experience, in response to an intervention, environmental modification, or as a result of learning. Ramon y Cayal speculated that plasticity involves changes in the dendrites and

interneuronal connections in the cortex (DeFelipe & Jones, 1988). Although brain structure determines which areas will influence the firing of another, brain activity can also change structure by strengthening or weakening connections through experience-dependent plasticity mechanisms over time (Kandel, et al., 2000). Neuroplastic changes to the cortex has been associated with skill level and acquisition. A notable example is the London taxi drivers study (Maguire, Gadian, Johnsrude, Good, Ashburner, Frackowiak, & Frith, 2000). This study found greater hippocampal volume in London's taxi drivers, reflecting their expertise in spatial navigation. Another study on zen meditators found greater cortical thickness in areas associated with regulating pain sensitivity (dorsal anterior cingulate cortex) and somatosensory cortices (Grant, Courtemanche, Duerden, Duncan, & Rainville, 2010). However, neuroplasticity can also create a state of vulnerability by exposing the cortex to the damaging effects of stress, resulting in cortical atrophy (Sapolsky, 2000). Generally, changes to cortical structure are also associated with functional changes; for example, reduced ACC activation is associated with reduced volume (Drevets, Price, & Furey, 2008).

1.3 Cortical Thickness

Cortical thickness refers only to the grey matter of the cortex. More specifically, it is the distance measured between the outer grey matter surface to the inner grey-white matter surface. The average thickness of the cortex is approximately 3.0 mm, but region-specific values range between 2.0 - 4.0 mm. Lerch (2001) identified 3 criteria for an anatomical definition of cortical thickness, as measured by MRI:

- i) Thickness is measured as the shortest path length between the two surfaces of grey matter, while following the surface curvature of the cortex.
- ii) Each point, or vertex, on the cortical surface is assigned one thickness value, with non-overlapping paths.
- iii) Thickness is a volumetric property of the cortical column.

Although the aim of a cortical thickness measurement is to reflect the cortical column, the 1 mm cubic resolution of MRI limits the approximation to the hypercolumn level (Mountcastle, 1997). Nevertheless, Lerch's (2001) operational definition of cortical thickness greatly improves upon previous methods, which relied on manual measurements. Instead, modern cortical thickness analysis applies the *Laplace equation* in a computational approach (Figure 1). Briefly, it is a harmonic function solved through a partial differential equation, resulting in one thickness value across the two surfaces of the cortex (Lerch, 2001).

Figure 1: Laplace Equation

$$\Delta^2 \Psi = \frac{\partial^2 \Psi}{\partial x^2} + \frac{\partial^2 \Psi}{\partial y^2} + \frac{\partial^2 \Psi}{\partial z^2} = 0$$

1.3.1 Relationship between brain size, volume, surface area and cortical thickness

As discussed above, larger brains, containing more neurons, result in greater expansion of surface area, sulcal depth, gyrification, and mean curvature, but is accompanied by only a slight increase in cortical thickness (Im, Lee, Lyttelton, Kim, Evans, & Kim, 2008). Thus, increases in neuronal number do not much affect the thickness of the cortical column. Furthermore, much of the increase in brain volume results in expansion of white matter, not grey matter (Zhang, 2000). Although there seems to be a sex effect on brain size, with male brains being 8 - 10% larger than females (Giedd, et al., 1996; Sowell, et al., 2006), this sex effect is due to a later peak in surface area in males than females, with no difference in peak cortical thickness (Raznahan et al., 2011). Thus, the effect of sex on cortical thickness is negligible after controlling for brain volume (Im, et al., 2008).

Cortical volume is confounded by two genetically and evolutionarily distinct properties: cortical thickness and surface area (Panizzon, et al., 2009; Hutton, et al., 2009; Raznahan et al., 2011). As each of these measurements represent different aspects of neuroanatomy it is difficult to compare groups differing in disease status using cortical volume. Thus, Panizzon and colleagues (2009) recommend against using cortical volume as an endophenotype for a disorder. Another advantage of cortical thickness over volume is that it uses a surface-based method of registration across subjects, controlling for differences in surface topology (Van Essen, et al., 1998). Furthermore, thickness better reflects underlying connectivity than volume and in

distinguishing between patient groups from healthy controls (Jiao, Chen, Ke, Chu, Lu, & Herskovits, 2010). Finally, cortical thickness, as an index of the cortical column, is an easier concept to interpret than volume, which has no direct neurobiological correlate (Singh, et al., 2006; Mangin, Jouvent, & Cachia, 2010).

In the past 10 years, interest in cortical thickness has been resurrected using MRI and the emergence of automated methods for segmenting and quantifying brain structural characteristics, and the complementary statistical tools to visualize 3D spatial maps (Takao, Abe, & Ohtomo, 2010). Several studies comparing voxel-based morphometry (VBM), surface-based morphometry (SBM) and cortical thickness (CT) measurements have supported CT as the most sensitive measure of cortical structure (Im, Lee, Lyttelton, Kim, Evans, & Kim, 2008; Fjell & Walhovd, 2010; Hutton, Draganski, Ashburner, & Weiskopf, 2009; Singh, Chertkow, Lerch, Evans, Dorr, & Kabani, 2006). Well validated cortical thickness algorithms have been developed to automate the processing of large datasets, with the advantages being reproducibility of results, improved objectivity, and reduced labour-intensity of manual methods (Fischl & Dale, 2000; Lerch and Evans, 2005; Lerch, Worsley, Shaw, Greenstein, Lenroot, Giedd, & Evans, 2006; Dickerson, et al., 2008).

1.3.2 The effect of age on cortical thickness

The general pattern of normal aging on the cortex involves overall thinning of the cortical mantle, widening of sulci, and expansion of the ventricular system (Fjell &

Walhovd, 2010). However, there are region specific differences in the timing of the peak thickness, decline, and degree of change; For example, some areas show a late peak and steady linear decline (e.g. prefrontal cortex); others have a rapid, non-linear decline (e.g. orbitofrontal cortex); the posterior temporal cortex increases in thickness and peaks later in life (age 30 years) followed by a rapid decline (Sowell, Peterson, Thompson, Welcome, Henkenius, & Toga, 2003). There are also sex-specific maturational changes resulting in separate peaks in thickness (Giedd, et al., 1996; Shaw, et al., 2008). Maturational changes in cortical thickness can be detected within one year on MRI with reductions between 0.5% and 1.0% (Fjell & Walhovd, 2010). A twin study (van Soelen, et al., 2012) showed that the extent and rate of cortical thinning is influenced by genetics (Raznahan, et al., 2011). In addition, pre- and post-natal developmental events can also influence the thickness of the cortex. For example, abnormalities in cholinergic innervation during development has been shown to reduce cortical thickness (Jungerman, Lucassen, & Francis, 2011).

1.3.3 *Reliability*

Automated algorithms measuring cortical thickness are sensitive (Lerch & Evans, 2005) and specific (Lerch, Pruessner, Zijdenbos, Collins, Teipel, Hampel, & Evans, 2008), making it useful in the study of neuropsychiatric illness. It has also been used to construct predictive models, for example using machine learning, to distinguish cases from healthy controls (Jiao, et al., 2010). Across scanners of varying manufacturers, field strength, and across sessions, cortical thickness measurements are highly reliable

(Han et al., 2006; Dickerson, et al., 2007). However, one study found that 3T scanners are slightly biased to be thicker than 1.5T, thus recommending that caution should be taken in comparing cortical thickness from scans obtained from scanners of different field strength (Han, et al., 2006). Variation in pulse sequence also has an impact on test-retest reliability (Han, et al., 2006). Cortical thickness has also been validated as a reliable correlate of cognitive function in both localization and magnitude (Dickerson, et al., 2007). Taken together, given the high reliability of cortical thickness measurement, it is quite possible to pool data from different sources in multicenter studies, creating larger sample sizes.

Sample size estimates for cross-sectional studies comparing psychiatric groups with healthy controls depend on the size of the difference and measurement error (%). At a significance level of $p < 0.05$, one-sided, and statistical power of 0.9, a difference of 0.2 mm can be detected with group sizes of 7 subjects per group (Han, et al., 2006). Of course, statistical analyses still require a minimum of 10 - 15 observations per predictor variable used in the general linear model equation (Babyak, 2004). *A priori*, region-of-interest (ROI) analyses result in better prediction accuracy than whole-brain exploratory analyses (Chu et al, 2012) and minimizes penalty for multiple comparisons.

1.4 Review of cortical thickness applied to major depressive disorder

Table 1 provides a literature review of all the studies on cortical thickness in MDD. To date, there are a total of 7 cortical thickness papers studying the MDD

population. One study focused solely on pediatric MDD and included a group of patients with obsessive-compulsive disorder (OCD) as a psychiatric control (Fallucca, et al., 2011). Another study focused solely on persons at-risk for MDD by virtue of a family history, but otherwise were healthy individuals (Peterson, et al., 2009). This study included both adults and children. Three studies included late-life depressed patients (Koolschijn, van Haren, Schnack, Janssen, Pol, & Kahn, 2010; Colloby, Firbank, Vasudev, Parry, Thomas & O'Brien, 2011), with one focusing on minor depression (Kumar, Ajilore, Zhang, Pham, & Elderkin-Thompson, 2012). Most studies were cross-sectional, however, one longitudinal study had a re-scan at 6-month follow-up, or at remission (Järnum et al, 2011). The methods used to measure cortical thickness included FreeSurfer (Fischl & Dale, 2000), Constrained Laplacian Anatomic Segmentation using Proximity (CLASP; Kabani, Le Goualher, MacDonald, & Evans, 2001; Kim, et al., 2005), and Fast Accurate Cortex Extraction (FACE; Eskildsen, Uldahl & Østergaard, 2005), all of which are surface-based techniques.

Table 1: Literature review summarizing all of the cortical thickness studies conducted in the MDD population, to date.

Author	Year	Participants	Age mean (SD)	Number of episodes	Duration of illness (months)	Cortical thickness method	Results
Peterson	2009	66 At-risk (12 children, 54 adults), 65 HC (31 children, 34 adults)	Children under 18, adults ranged from 18-54	n/a	n/a	FreeSurfer	Thinning in lateral surface of R hemisphere (inferior and middle frontal gyri, somatosensory, motor cortex, dorsal and inferior parietal, inferior occipital gyrus, posterior temporal); Thickening in subgenual ACC, PCC, medial orbitofrontal cortex
Koolschijn	2010	28 female late-life MDD, 38 HC	64.04 (10.90); average age-of-onset = 33 (9.48)	11.14 (14.12); range 1-49; median = 4	93.50 (17.50)	CLASP	No differences in cortical thickness between groups, no effect of illness duration, severity, or number of episodes
Jarnum	2011	23 MDD, 26 HC	43 (9.9)	2.1(1.8)	not reported	FACE	Baseline: thinner orbitofrontal, superior temporal gyrus, insular cortex between groups; Thinner posterior cingulate in non-remitters than remitters; Follow-up: thinner orbitofrontal at baseline
Fallucca	2011	24 paediatric MDD, 24 OCD, 30 HC	13.96 (2.41)	not reported	24.90(31.32)	FreeSurfer	Regions thinner in depressed vs. controls: R pericalcarine gyrus, R post-central gyrus, R superior parietal gyrus, L supramarginal gyrus; Regions thicker in depressed vs. controls: R and L temporal poles
Colloby	2011	38 late-life MDD, 30 HC	74.1 (6.1); First-onset 51.8 (22.3)	not reported	276.0(258.0)	FreeSurfer	No significant differences in cortical thickness in frontal lobes (ROI) between groups
Kumar	2012	16 minor late-life depression, 16 HC	76.25 (7.54)	1 subject had a previous episode of MDD	12/16 had duration longer than 2 years	FreeSurfer	Thinner R cingulate cortex (isthmus) between groups
Lim	2012	45 late-onset MDD, 47 HC	71.8(4.8)	not reported	15.6(6.0)	FreeSurfer	Thinner rostral ACC, mOFC, DLPFC, superior and middle temporal gyrus, and PCC in MDD compared to HC

HC = Healthy control

MDD = Major depressive disorder

OCD = Obsessive-compulsive disorder

SD = Standard deviation

CLASP = Constrained Laplacian Anatomic segmentation using Proximity

FACE = Fast Accurate Cortical Extraction

R = Right

L = Left

ACC = Anterior cingulate cortex

PCC = posterior cingulate cortex

mOFC = medial orbital frontal cortex

OFC = orbital frontal cortex

ROI = Region of interest

EOD - Early-onset depression

LOD = Late-onset depression

In general, findings mostly describe decreases in thickness in the MDD group compared to healthy controls, although there are also reports of regional increases in thickness in the the early-MDD populations. Early-life MDD and family history seems to be associated with the largest differences in cortical thickness, affecting a larger expanse of the cerebral cortex. Furthermore, many of the areas that are being reported in these groups do not fit the conventional cortico-limbic regions widely reported in the functional and volumetric literature. For example, cortical thinning in right lateral parietal cortex was found to mediate familial risk for depression via poor performance on tasks assessing attention for social and emotional stimuli (Peterson et al., 2009). Cortical thickness in late-life MDD, on the other hand, is not considerably different from age-matched healthy controls. One study found no differences in a sample of late-onset patients compared to controls, and no effect of illness duration, number of episodes, or depression severity (Koolschijn, et al., 2010). These findings may support a separate pathophysiological mechanism of late-life MDD, possibly involving white-matter (Sheline, et al., 2010) or subcortical abnormalities (Burke, McQuoid, Payne, Steffens, Krishnan, & Taylor, 2011). In contrast, early-life MDD and family history of MDD both involve extensive changes to the cortical mantle, possibly reflecting developmental processes, as these changes appear very early in life. The limited and inconsistent evidence in the current literature is suggestive of differences between early- and late-life MDD, however, small sample sizes and confounding variables limits the interpretation of these findings.

Chapter 2

2.1 Early- and late-onset depression

The timing of the onset of major depression is an important consideration as several studies have discovered key differentiating characteristics between those patients presenting with an early age-of-onset compared to depression with a late-life onset. On average, the first onset of a major depressive episode occurs between the ages of 25 - 32 years (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005). In the STAR*D study, the average age-of-onset in patients who experienced their first depressive episode before the age of 18 was 12.4 years, and the average age for those experiencing their first onset after the age of 18 was 32.4 years (Zisook et al., 2004).

A consistent finding in the literature that differentiates early-onset depression (EOD) from late-onset depression (LOD) is that of family history, such that EOD is more likely to be associated with a family history of MDD (Peterson et al., 2009). Having a biological parent with MDD increases the risk in offspring by threefold (Williamson, Birmaher, Axelson, Ryan, Dahl, 2004). A longitudinal study (Weissman, Wickramaratne, Nomura, Warner, Verdeli, Pilowsky, & Grillon, 2004), spanning three generations, followed MDD patients, their children, and their grandchildren. They found an effect of familial loading, whereby offspring with both a parent and a grandparent with MDD were at a higher risk of developing a psychiatric illness relative to either offspring of a depressed parent alone, or a depressed grandparent alone (Weissman, et al., 2004). Furthermore, there seems to be a trend toward decreasing age-of-onset with each successive birth cohort, with the more recent generations experiencing depression at a

younger and younger age (Lavori, Warshaw, Klerman, Mueller, Leon, Rice, & Akiskal, 1993).

In terms of symptomatology, characteristics that distinguish EOD from LOD include more suicide attempts, sadness, irritability, neuroticism, childhood-onset anxiety disorders, and atypical symptoms in EOD (Zisook, et al., 2004; Korten, Comijs, Lamers & Penninx, 2012). There is also a higher female prevalence and longer duration of illness (including more episodes and longer duration of episodes) in EOD. In fact, Zisook and colleagues found greater duration of illness in EOD patients, even after adjusting for current age. There are also differences in the clinical trajectories of EOD and LOD. Several studies have indicated that patients with EOD have poor outcomes, including poor response to antidepressant treatment, greater illness severity, and a higher relapse rate (Kemp, Gordon, Rush & Williams, 2008; Heim, Plotsky & Nemeroff, 2004; Dekker, Ferdinand, van Lang, Bongers, van der Ende, & Verhulst, 2007). Gollan and colleagues (2005) analyzed the course of recovery in EOD and LOD in a prospective study with a two year follow-up period. EOD patients maintained a higher level of residual symptoms over the two years, and had a higher rate and shorter period to relapse than the LOD group (Gollan, Rafferty, Gortner, & Dobson, 2005). Less is known about neuroanatomical differences, although a consistent finding in depression occurring in the elderly (*i.e.* after age 60) is that of white-matter hyper-intensities, also known as vascular depression (Sheline, et al., 2010).

Definitions of EOD in the literature have been inconsistent in their age cut-offs, which range between 18 - 60 years. EOD includes childhood-onset and adolescent-onset depression, however, with a lack of consensus on the upper age-limit, a comparison of studies will result in inconsistent findings. Some studies defined early-onset, as “pre-adult” and thus used the age of 18 as a cut-off (Zisook et al, 2004; Gollan et al., 2005). However, this “pre-adult” age cut-off may be arbitrary, especially for a sensitive analysis of cortical thickness, which is known to be affected by developmental processes (Sowell, Peterson, Thompson, Welcome, Henkenius, & Toga, 2003). Another study used a cut-off of 40 years to differentiate EOD from LOD using a biologically-based criteria; their rationale being that there is an association between MDD onset after age 40 and an increased risk for co-morbid vascular disease (Korten, Comijs, Lamers & Penninx, 2012). A cut-off of 25 years was shown to differentiate EOD from LOD based on family history (Kendler et al., 2005). Similarly, a study in bipolar disorder showed differences in cortical gyrification between early-onset (cut-off of 25 years) and intermediate-onset (age 25-45 years) (Pentilla et al., 2009). This study considered late-onset bipolar disorder to occur after the age of 45. However, studies that use the cut-off of 40 years ignore an important distinction between adolescent- and adult-onset MDD. In addition, some brain structures, including the prefrontal cortex, are still in the process of development into the early-20's (Segalowitz & Davies, 2004). Thus, a cut-off of 25 years most likely reflects an age-cut-off that is sensitive to the neurodevelopment of the cerebral cortex.

In summary, EOD and LOD differ in their genetic origins, symptomatology, course, and prognosis, which may translate to distinctions in their neurobiology. Despite these differences, early- and late-onset MDD are still subject to the same diagnostic criteria and treatment strategy. Few studies have used age-of-onset as a grouping factor, which may account for some of the heterogeneous results seen in studies of MDD. There are no studies that investigate the influence of age-of-onset on cortical thickness in MDD. However, there is growing evidence suggesting that the neurobiological mechanisms underlying the development of EOD and LOD may differ.

1.2 Neurotoxicity hypothesis

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is strongly implicated in the pathophysiology of MDD. Higher basal cortisol levels upon awakening and failure on the dexamethasone suppression test in MDD patients identify abnormal functioning of the homeostatic mechanisms that normally shut off the stress response (Vreeburg, et al., 2009). It has often been observed that periods of elevated stress precede the onset of a major depressive episode (Kendler et al., 2005). Generally, it is accepted that risk for MDD arises as a stress-diathesis, whereby genetic risk interacts with environmental stressors (Caspi et al., 2003). Stressors can take various forms, such as poverty, unstable family environment, natural disasters, war, and chronic illness. However, early-life stress, especially physical, sexual, and emotional abuse, may have a particularly unique influence and is hypothesized to constitute a distinct neurobiological subtype of MDD (Heim, Plotsky, & Nemeroff, 2004).

The mechanism by which stress increases the risk for developing MDD may involve neurodegeneration (Sapolsky, Krey, McEwen, 1986). Although the stress response is an adaptive mechanism that protects an organism from threat, over-activity of the system can lead to neural damage and loss (McEwen, 2005). Translating these findings to the etiology of MDD leads to the suggestion that MDD patients are in a state of chronic stress that cannot be turned off, resulting in neurodegeneration of neural structures that regulate stress and emotion (McEwen, 2005).

Sapolsky, Krey, and McEwen's "glucocorticoid cascade hypothesis" (1986) provides an account of how HPA axis dysregulation leads to neurodegeneration via glucocorticoid's effects on downstream cellular systems. Briefly, cumulative exposure to stress hormones results in tissue degeneration in brain regions that normally inhibit the HPA axis by a negative-feedback mechanism. Consequently, excess levels of circulating stress hormones continue to be secreted at high levels. This feed-forward cascade predicts that, over time and repeated activation, the brain's ability to maintain allostasis decreases and that chronic stress can accelerate the degenerative process. Glucocorticoid receptors (GR) are expressed in limbic regions that are also involved in the negative-feedback loop inhibiting HPA axis activity, such as the amygdala and the prefrontal cortex, however, the hippocampus is especially sensitive to the effects of stress, given its high density of GR receptors (DeKloet, Vreugdenhil, Oitzl, & Joels, 1998). Mechanisms of hippocampal atrophy include reduction in dendritic branching, suppression of neurogenesis, decreased rate of neuron survival, and permanent neuron loss (Vyas, Mitra, Shankaranarayana, & Chattarji, 2002; Stockmeier et al., 2004).

Structural atrophy of prefrontal cortex and amygdala, however, involve reductions in glial cells and neuronal restructuring, as opposed to neuronal degeneration (Rajkowska et al., 1999; Sheline, Gado, & Price, 1998; Vyas, et al., 2002).

Glucocorticoid receptors are located in the cytosol and translocate to the nucleus upon activation, where they can act as transcription factors. This pathway can result in either up- or down-regulation of inflammatory proteins and neurotrophins (Kumar & Thomson, 1999; Alboni, et al., 2011). Glucocorticoids also affect neuromodulation and neurotransmitter systems through their non-genomic actions via activation of the N-methyl-D-aspartate (NMDA) receptor on the plasma membrane (Xiao, Feng, & Chen, 2010). This pathway results in an increase in excitatory neurotransmitter release, namely glutamate (Moghaddam, Boliano, Stein-Behrens, & Sapolsky, 1994). Xiao and colleagues (2010) showed that co-exposure of hippocampal neurons to glucocorticoids and various NMDA-receptor agonists resulted in neuronal death, but not when NMDA was administered on its own. Second-messenger systems are also activated through this pathway, increasing the release of free radicals and other toxic by-products (Howard, Nakayama, Brooke, & Sapolsky, 1999). Thus, continuous activation of excitatory neurotransmitters can lead to excitotoxicity, which is known to contribute to neuronal degeneration (Kim et al., 2011).

Several convergent lines of evidence have shown that hippocampal volume is reduced in patients with MDD (Sapolsky, 2000; MacQueen, et al., 2003; McKinnon, Yucel, Nazarov, & MacQueen, 2008; Stockmeier et al., 2004). However, this effect is not

unique to depression, as reduced hippocampal volume has also been found in other stress-related illnesses, such as PTSD and schizophrenia (Geuze, Vermetten, & Bremner, 2005). In patients with MDD, hippocampal volume is related to duration of illness, where patients who experienced more than one episode of depression for a duration longer than two years showed reduced volumes (McKinnon, et al., 2008). This supports the neurodegenerative model, which would predict that smaller hippocampal volume is a result of cumulative stress or years with depression. The prefrontal cortex is also a known target of cortical atrophy in depressed patients (Rajkowska et al., 1999). Decreased cortical gyrification index, quantified as a ratio between the total sulcal area and the area of exposed gyri, is another marker of neurodegeneration that has been identified in first-episode patients with a mid-life onset of depression (Zhang, Yu, Zhou, Li, Li, & Jiang, 2009).

Although stress is undoubtedly an important factor in triggering a first major depressive episode, MDD is often not a one-time occurrence. In fact, multiple relapses are common in the course of illness, where each depressive episode increases the probability of a subsequent episode (Monroe & Harkness, 2005). This phenomenon, where the experience of a depressive episode itself leads to vulnerability to further episodes, has been described as kindling (Duman, Heninger, & Nestler, 1997). Similar to the kindling theory of epilepsy, where sub-threshold electrical stimulation of neural tissue leads to progressive lowering of the membrane potential threshold, increasing the likelihood of eliciting a seizure, experience-dependent brain changes due to stress can lower the “threshold” for experiencing a future depressive episode (Post, Weiss, &

Leverich, 1994). Indeed, with increasing episodes the impact of stressful life events has less relevance in the cause of relapse, such that depression may precipitate spontaneously (Kendler et al., 2001). Kendler and colleagues (2001) also tested the effect of genetic risk and number of previous episodes on the occurrence of a new depressive episode in a twin study. They found that having had previous episodes was only predictive of a subsequent episode in those with a low genetic risk. Those with high genetic risk were more likely to have an onset of depression that was not triggered by any significant stressor or preceded by previous episodes. Thus, previous episodes are not the only form of kindling and genetic risk may have a “pre-kindling” effect.

The kindling phenomenon may be due to incomplete reversal of the changes that follow the impact of stress on the brain. This hypothesis is supported by the observation that even after remission from antidepressant treatment, some patients still suffer from persistent sub-threshold symptoms, which may reflect enduring changes to the underlying neural circuitry (Bhagwagar & Cowen, 2008). Furthermore, EOD patients exhibited more sub-threshold symptoms and a shorter duration in between episodes compared to LOD patients (Gollan et al., 2005). Even when matching for age, EOD patients experienced depression for a longer period of time. These results were explained by a “stage of illness hypothesis”—EOD patients were farther along in the progression of the illness than patients with LOD (Post et al., 1994).

Interestingly, glucocorticoid levels have also been found to be higher in Alzheimer’s patients than age-matched controls (Ferrari, Fioravanti, Magri, & Solerte,

2006), and there is an association with depression preceding the onset of Alzheimer's disease (Harwood, Barker, Ownby, & Duara, 1999; Sotiropoulos, et al., 2011).

Furthermore, onset of depression in early-life is more likely to lead to Alzheimer's and other forms of dementia than late-onset depression (Byers & Yaffe, 2011). Premature cognitive deficits in memory and executive function are also commonly observed in MDD, and remain even in remission (Hasselbalch, Knorr, & Kessing, 2011), which may reflect the effects of accelerated neurodegeneration through the shared mechanisms of neuro-inflammation and decreased neurotrophic support (WuWongse, Chang, & Law, 2010). Taken together, these data have led to the suggestion of a "final common pathway" theory, where neurodegeneration is considered a hallmark of neuropsychiatric illness (Henn & Vollmayr, 2004).

Holtzheimer and Mayberg (2011) recently proposed a re-definition of MDD that falls in line with the above hypotheses; this model emphasizes the role of disruption in homeostasis in which the system becomes unable to regulate emotion following a perturbation. Given the prevalence of recurrences and treatment-resistance, it is clear that conventional treatments, which aim to bring the patient out of the negative mood state, are not addressing the underlying pathophysiology. The authors hypothesize that non-response to treatment occurs because the homeostatic system has established a new set-point at a pathological level (*i.e.* negative mood state), and non-response reflects an inability to return to baseline mood levels, which they termed being "stuck in a rut". This re-setting of the set-point may be analogous to the re-structuring of the

HPA-axis following prolonged exposure to stress, but may also involve re-setting of emotion regulation pathways.

In summary, the pathophysiology of MDD may develop in response to repeated stressful events, triggering a first episode of depression. This event fundamentally alters the emotion regulation circuitry, with neuronal and regional remodeling of neural structures, making the system more vulnerable to subsequent episodes. With age, the systems that counteract stress get weaker, and episodes are more likely to occur in response to mild stressors, or spontaneously. The neurodegeneration and neurotoxicity models of MDD explain the development and progression of illness, which may lead to LOD; however, they do not fully explain the occurrence of, seemingly spontaneous, early-onset of MDD in the absence of a significant stressor.

1.3 *Vulnerability hypothesis*

Another way to explain the differences between EOD and LOD is the vulnerability hypothesis, which posits that EOD may be of neuro-developmental origins. This hypothesis predicts that EOD patients possess pre-existing risk genes or experiences of early adverse events that predisposes them to developing MDD, rather than the accumulation of neuronal damage over time (Lupien, McEwen, Gunnar, & Heim, 2009). In contrast to the neurodegeneration hypothesis, the vulnerability hypothesis would predict that reduced hippocampal volume is a pre-existing risk factor in stress-related disorders, that is present well before the onset of symptoms. A pertinent example is the

twin study of Vietnam war veterans; Hippocampal volumes in trauma-exposed twins were similar in size to their non-exposed counterpart. Veteran twins with smaller hippocampal volumes were more likely to suffer from post-traumatic stress disorder (PTSD) than veteran twins with larger volumes (Gilbertson, Shenton, Ciszewski, Kasai, Lasko, Orr, & Pitman, 2002). The pre-existing small volume of the hippocampus can be attributed to genetics because monozygotic twins share 100% of their genes. Thus, reduced hippocampal volume seems to be a risk factor that is antecedent to the trauma, rather than a consequence of trauma.

Certain personality traits contribute to vulnerability to depression, many of which also share a genetic component. Neuroticism, characterized by the tendency to experience negative mood states and heightened stress reactivity, has been identified as a trait marker of depression (Harro & Kiive, 2010). Genome-wide association studies have linked neuroticism to a single-nucleotide polymorphism in the synaptosomal associated protein 25 gene (SNAP-25; Terracciano, et al., 2008). SNAP-25 plays a role in synaptic plasticity by controlling the release of neurotransmitters at synapses. It's specifically involved in increasing inhibition by interacting with calcium channels (Verderio, et al., 2004). Aside from MDD, SNAP-25 has also been associated with attention-deficit hyperactivity disorder (ADHD) and bipolar disorder, where higher expression levels in the prefrontal cortex is thought to modulate attention (Kim, et al., 2007; Etain, et al., 2010). In addition, both the short variant of the serotonin transporter gene (5HTTLPR) and the Pro variant of the GABA receptor subunit (Pro385Ser) have been associated with higher neuroticism scores (Sen, et al., 2004).

In addition to personality, research has identified various cognitive styles that are prodromal to the onset of depression. Based on Aaron Beck's (1979) cognitive theory of depression, the cognitive vulnerability theory predicts that an individual's cognitive response style confers risk for developing depression. Prospective studies have shown that individuals at high-risk, based on scoring high on cognitive style questionnaires (e.g. Response Styles Questionnaire), have 3-7 times greater odds of developing depression than low-risk individuals (Alloy, Abramson, Whitehouse, Hogan, Panzarella, & Rose, 2006). Studies of adolescents with a family history of depression, longitudinal studies on the course of residual symptoms, and the symptoms that precede an episode of depression, have elucidated a depressive "cognitive profile". This profile consists of cognitive tendencies to selectively process and store negative stimuli (Hamilton & Gotlib, 2004). Even neutral stimuli are affectively tagged with a negative bias. For example, one study found that hyperactivity in the amygdala during the encoding of emotionally-neutral stimuli is a trait response in MDD as it is present during a depressive episode and during remission (van Eijndhoven, van Wingen, Fernández, Rijpkema, Verkes, Buitelaar, & Tendolkar, 2011). Baseline amygdala activity is also hyperactive in MDD patients, suggesting that stimuli do not need to be emotionally-salient to be processed as such (Drevets, 2003). Whereas healthy participants interpret neutral faces as happy, depressed participants display a negativity bias, interpreting neutral faces as sad (Gollan, Pane, & McCloskey, 2008). Furthermore, the negativity bias also extends to attention for negative interpersonal stimuli (Gotlib, Krasnoperova, Yue, & Joormann, 2004), and negative face processing (Jacobs, et al., 2011).

Adolescents at risk for depression display negative attributional style and self-perception involving increased negative self-focus (*e.g.* attributing negative events and personality traits to the self) and maladaptive rumination, which are proximal predictors of depression onset (Jacobs, Reinecke, Gollan, & Kane, 2008). Rumination is a process by which an individual excessively engages in negative self-focused thinking (Nolen-Hoeksema, 2000). This self-referential processing is associated with hyper-activation of medial prefrontal cortex (mPFC). Whereas dorsal lateral prefrontal cortex (DLPFC) activity increases following antidepressant treatment, indicating that more effortful cognitive control is required for depression remission, mPFC activity remains elevated despite treatment (Lemogne, et al., 2010). This suggests that hyperactivity in the mPFC is a trait-like characteristic of MDD that may mediate vulnerability to future episodes.

There are also abnormalities in information processing. Poor performance on tasks assessing attention for social and emotional stimuli was correlated with greater depression severity and predicted life-time rates of MDD in a sample with a family history of MDD (Peterson et al., 2009). Euthymic patients in remission also perform worse on tasks of attentional shift, Stroop tasks and sustained attention (Paelecke-Habermann, Pohl, & Leplow, 2005). On the affective Go/No-Go task, adolescents in their first-episode of depression exhibited a marked bias towards negative stimuli, shown by faster responding to negative and slower responding to positive, suggesting that attention to negative information is more readily processed (Kyte, Goodyer, & Sahakian, 2004).

Closely related to attention, is the default-mode network (DMN), which is shown to be anti-correlated with task-positive networks (*i.e.* networks engaged in cognitive tasks) (Broyd, Demanuele, Debener, Helps, James, & Sonuga-Barke, 2009). This network engages the same structures as self-referential processing, namely the cortical midline structures (CMS): mPFC, and the posterior cingulate cortex (PCC) (Lemogne, Gorwood, Bergouignan, Pelissolo, Lehericy, & Fossati, 2011). Depressed patients have been shown, in one study, to exhibit greater resting-state connectivity of DMN with the subgenual anterior cingulate cortex and thalamus, which the authors hypothesize may decrease the capacity of the system to switch to more dorsal-lateral, task-positive networks (Greicius, et al., 2007). This inability to switch attention from introspective thinking to external tasks is proposed to underly the mechanism of rumination. Another study demonstrated that depressed patients also have difficulty on the Wisconsin Card Sorting Task, suggesting that there may also be increased perseveration (Merriam, Thase, Haas, Keshavan, & Sweeney, 1999). Whitmer & Banich (2007) found that depressive ruminators perseverate on information at hand, with an inability to switch attention to effectively acquire new information.

Other candidate risk genes will likely be involved in HPA-axis regulation, intracellular cascades of monoaminergic neurotransmission and cell survival pathways, and emotion regulation circuitry. The corticotropin-releasing hormone type 1 receptor (CRHR1) has been found to protect individuals who have experienced early childhood abuse from depression, thus, the absence of this gene variant likely increases vulnerability when in combination with environmental stress (Polanczyk, et al., 2009).

The Met variant of the brain-derived neurotrophic factor (BDNF) and the s variant of the serotonin transporter (5HTTLPR) gene (Duman, Heninger, & Nestler, 1997) are also risk factors identified in MDD. Both of these genes are stress-responsive; there is direct evidence from animal studies showing that stress modulates BDNF expression via the cAMP response element binding protein (CREB) pathway, where restraint stress leads to inactivation of these pathways and down-regulation of BDNF expression (Alboni, et al., 2011). Likewise, the serotonin transporter gene confers risk for depression by enhancing cortisol reactivity (Gotlib, Joormann, & Minor, 2007). Early life stress also interacts with individuals carrying the CC variant of the HTR3A receptor, resulting in greater grey matter loss in cortico-limbic regions, specifically the hippocampus and prefrontal cortex (Gatt, et al., 2010). Finally, individual differences in levels of the 5-HT1A autoreceptors in the raphe nucleus also affects stress reactivity; increased expression of these receptors lead to decreases in serotonergic tone via projections to forebrain areas (Richardson-Jones, et al., 2010).

In addition to interactions with stress, these risk genes also interact with one another. In combination with early life stressors, the epistatic effect of the s allele of 5HTTLPR and the BDNF met allele increases emotional reactivity as evidenced by elevated heart rate, greater negativity bias, and right frontal lobe asymmetry (Gatt, Nemeroff, Schofield, Paul, Clark, Gordon, & Williams, 2010). This interaction has also been linked to impairments in executive function and emotion processing (Wang, Ashley-Koch, Krishnan, & Taylor, 2012). Thus, early experience may shape the manner in which the system responds to stress, increasing reactivity which seems to be

maintained into adulthood. These enduring changes are seen at both the neuroendocrine and behavioural level.

Highly conserved gene networks provide the neural “blueprint” upon which development of initial brain architecture is based, however, experience soon takes over as the critical factor for determining the switching “on” and “off” of certain functions (Katz & Shatz, 1996). Gene expression can be modulated by the presence or absence of environmental stressors, resulting in a gene x environment interaction known as epigenetic modification. This has been shown to affect the developmental trajectory of brain circuitry regulating stress reactivity and emotion in rats; For example, behaviorally-induced increases or decreases in methylation and transcription factor binding to the promotor region of the glucocorticoid receptor, by the presence or absence of sensitive maternal parenting, affects levels of expression of these receptors and thus programming of the HPA axis (Weaver, et al, 2004). In humans, early childhood abuse also has programming effects as evidenced by decreased mRNA expression of the glucocorticoid receptor (NR3C1) in abused suicide victims (McGowan, et al., 2009). Thus, genes provide a neural “scaffolding” upon which later experiences build upon, shape, and refine (Fox, Levitt, & Nelson, 2010).

Stressful events during the course of development can have significant programming, differentiating, maintenance, and manifestation effects, depending on the timing of those events (Lupien, et al., 2009). Periods of development (*i.e.* infancy and early childhood) and decline (*i.e.* old age) seem to be particularly sensitive time frames

as they are periods characterized by dynamic change, increased neuroplasticity, and are thus sensitive to changes in neuronal structure.

Early childhood trauma is associated with disruptions to hippocampal development, which is in a period of rapid growth, resulting in small hippocampal volumes when measured in adulthood (Andersen, Tomada, Vincow, Valente, Polcari, & Teicher, 2008). The effects of a small hippocampus, in turn increases CRH-driven spine reduction in the hippocampus, modulating HPA activity, and increasing reactivity to stress (Chen, Dubé, Rice, & Baram, 2008). By contrast, stress experienced during adolescence is associated with reduced prefrontal volumes, a structure that is still in development during this period (Andersen, et al., 2008). Animal studies have shown that stress during adolescence impacts prefrontal cortical and amygdala structure, altering 5-HT levels, and behavioural responses to stress (Raftogianni, Diamantopoulou, Alikaridis, Stamatakis, & Stylianopoulou, 2012). There is also evidence that there are differentiating effects of time of trauma on the development of either PTSD or major depression; Women who experienced trauma before the age of 12 are at an increased risk for both major depression and PTSD, whereas women who experienced trauma between 12-18 years more often developed PTSD (Maercker, Michael, Fehm, Becker, & Margraf, 2004). This finding may be explained by the maturation of areas supporting development of the HPA-axis and mood regulation pathways in early childhood, and prefrontal regions in adolescence, corroborating the notion that different structures are impacted depending on the age at which the trauma occurred.

Adolescence is a particularly sensitive period as it is marked by heightened basal levels of circulating hormones, including growth hormones, sex hormones, and cortisol. Sex hormones, in particular estradiol, interact with the HPA axis, creating a synergistic increase in cortisol levels (McCormick & Mathews, 2007). This may explain a lack of a discernible “trigger” in adolescent-onset depression, due to the heightened internal milieu of stress hormones, thus even small perturbations may lead to the precipitation of an episode. Puberty is also the point at which prevalence for depression between males and females diverge, where the risk of developing depression in females is twice that for males, and is accounted for by the onset of menarche (Patton, Hibbert, Carlin, Shao, Rosier, Caust, & Bowes, 1996).

In adults, the brain is in a state of stabilization and maintenance of existing connections and structures. Exceptions to this include the transition periods experienced by women around the time of pregnancy and menopause, which represent “windows of vulnerability” for depression onset (Lokuge, Frey, Foster, Soares, & Steiner, 2011). In older adults, mean diurnal levels of cortisol are again increased in comparison to younger adults (Raskind & Peskind, 1994). Stress induced reductions in dendritic branching is greatly affected in aging rats, and these effects do not recover over time, whereas young rats show a full recovery and reversal of this effect, which demonstrates the increased vulnerability of prefrontal structures to stress in aging (Janssen, McEwen, Morrison, & Bloss, 2010). The amygdala is also beginning to decline beginning in the sixth decade, and these maturational changes are hypothesized to experience the greatest impact by stress than any other regions (Lupien, et al., 2009). With respect to

limbic structures, neuroimaging studies have shown that hippocampus and amygdala grey matter volume are among the earliest structures to develop and then are late to decline compared to parahippocampus and cingulate cortices (Grieve, Korgaonka, Clark, & Williams, 2011). These structural changes parallel the cognitive decline seen in the elderly, typically starting with memory loss and followed by executive functions (Fjell & Walhovd, 2010).

Furthermore, the mechanisms behind the morphological changes to the cortex may not involve actual loss of neurons in aging, as was once widely believed (Wickelgren, 1996). Rather the mechanism seems to be a combination of shrinkage of neurons, reduced neurogenesis, and changes to myelination and dendritic branching, while generally preserving the neuronal cell count (Terry, DeTeresa, & Hansen, 1987; von Bohlen und Halbach, 2010). This is in contrast to stress during development which results in reduced neuronal cell counts, mediated by either reduced neurogenesis or increased apoptosis. (Mychasiuk, Gibb, & Kolb, 2012). There is evidence that stress attenuates neurogenesis in adult hippocampus, therefore, opportunities to develop depression in adulthood may arise due to plasticity of the brain (Duman & Monteggia, 2006).

To summarize the above literature, Hasler & Northoff (2011) described a heuristic model underlying the risk for depression. This model shows how risk genes (genotype) affect the neurodevelopmental programming of key structures or circuits (endophenotype) that gives rise to alterations in emotion regulation, information

processing, and attention (behavioural phenotypes). Given these high-risk conditions, when the system is impacted by stress, psychiatric illness is likely to result. Thus, depression emerges as the cumulative effects and interactions of many genes with the environment, where early life stress plays a particularly potent role. For example, research on attachment theory has shown how secure or insecure attachment, independent of genetically-driven temperament, can alter HPA axis reactivity (Beatson & Taryan, 2003), leading to the downstream effects of maladaptive cognitive styles, and impaired neuropsychological function, all interacting to give rise to risk for depression.

Integrating the gene x environment interactions in the framework of the vulnerability hypothesis have lead to the search for endophenotypes of depression. In order to qualify as an endophenotype Gottesman (2003) has outlined 5 criteria: specificity, heritability, state-independence, co-segregation of the endophenotype and the illness within families, and presence in non-affected family members. Functional and structural characteristics of the brain have been proposed as possible endophenotypes (Peterson, et al., 2009). Some neuroimaging markers that have been identified are state-dependent, that is they change as a function of the mood state or in response to treatment. Examples of mood state-dependent structures whose activity or metabolism are modulated post-treatment include the DLPFC (Lemogne, et al., 2010) subgenual ACC (Mayberg, et al., 1997) and PCC (Järnum, et al., 2011). In contrast, the amygdala (van Eijndhoven, et al., 2011) and mPFC (Lemogne, et al., 2010) have been shown to precede illness onset and their effects persist into remission, indicating that they are trait-like characteristics. Regional cortical thickness, however, has been proposed as an

endophenotype of depression and has been shown to meet all 5 criteria, as demonstrated in a study with a genetic risk design (Peterson & Weissman, 2011).

In summary, the vulnerability hypothesis suggests that the combination of genetic and environmental risk factors play an important role in sensitizing the brain to future stressors by influencing neurodevelopment of the HPA-axis and emotion regulation circuitries. The evidence for this view, discussed in greater detail above, come from studies comparing high-risk with low-risk individuals in terms of family history (*i.e.* genetic vulnerability), and cognitive and information processing biases. Further evidence is derived from longitudinal studies following high-risk individuals, and studies of first-onset depression and depression remission. These studies demonstrate that certain symptoms are not simply epiphenomena of depression - they precede the onset and persist during periods of remission - therefore, it seems that the brain is fundamentally altered in high-risk individuals; remission does not entail that the brain returns to a normal state, comparable to a healthy brain. Finally, consistent with numerous studies linking family history with early-onset depression, high-risk individuals seem to be “pre-kindled” to develop depression at an earlier stage in life, compared to low-risk individuals who may require more years of stress and accumulation of allostatic load to develop depression (Kendler, et al., 2001).

2.4 Final Common Pathway

As research aiming to elucidate the central mechanism of depression progresses, it is becoming increasingly apparent that depression is heterogeneous; multiple neurotransmitters are involved, in distributed brain networks. Abnormalities in the networks that are responsible for the presence of many of the symptoms of depression have been well characterized (Drevets, Price, & Furey, 2008). We now know that mood disorders are more than simply chemical imbalances in the brain. The heterogeneity of the clinical profile suggests that there must be many factors involved in its etiology and many pathways by which the brain reaches the final outcome of depression. The final common pathway concept is the notion that although there may be several etiologies that give rise to depression, they must all converge onto a common neural pathway that manifests as depression (Akiskal & McKinney, 1973). There is value in discovering the final common pathway; such a conceptual framework can integrate the existing evidence, which may accelerate future research and the development of treatments (Stone, Lin, & Quartermain, 2009). Candidate final common pathways that have been proposed include the neurodegeneration hypothesis and have progressed to network hypotheses.

Observations of neurocognitive functional impairments and volume loss in the hippocampus and cortex of depressed patients have led to the hypothesis that crucial to the final common pathway of depression is neurodegeneration (Sapolsky, Krey, & McEwen, 1986). Proponents of this view cite the common finding that stress often precipitates a major depressive episode (Kendler, et al., 2001). Numerous studies have contributed to an extensive research literature corroborating the causal role of stress in

neurodegeneration (Vyas, Mitra, Rao, & Chattarji, 2002; Esch, Stefano, Fricchione, & Benson, 2002). By contrast, neurotrophins have a role in preventing degeneration, instead promoting neurogenesis, dendritic branching, and synaptogenesis (Duman & Monteggia, 2006). The cellular theory of depression (Duman, Heninger, & Nestler, 1997) - which focuses on the importance of neurotrophins - was proposed to explain the latency in antidepressant response, despite rapid increase in monoamine concentrations. This lag is due to the time it takes for intracellular cascades to become activated, most importantly the CREB pathway, which leads to BDNF expression. Studies have shown that neurogenesis is a requirement for the antidepressant response to take place (*e.g.* Santarelli, et al., 2003). A possible mechanism by which neurogenesis causes the antidepressant effect is through modulation of the HPA axis. By reinstating the negative feedback activity of the hippocampus, the HPA axis is better able to control the response to stress (Surget, et al., 2011). This theory also explains the reduced structure-function phenomenon. For example, hypoactivation and decreased volume of the DLPFC may be a result of decreased BDNF in this region, as its expression is activity-dependent (Dechant & Neumann, 2002).

Arguments against neurodegeneration as the final common pathway have also been proposed (Henn & Vollmayr, 2004); Firstly, not all antidepressants cause neurogenesis and secondly, neurogenesis is not necessary for an antidepressant effect to occur. Although electroconvulsive therapy (ECT) and antidepressant medications are associated with neurogenesis (Henn & Vollmayr, 2004), transcranial magnetic stimulation (TMS) is a therapy that produces antidepressant effects without also

increasing neuronal growth and proliferation (Czeh, et al., 2002). Thus, neurogenesis is not always correlated with clinical improvement in depressive symptoms. Furthermore, the theory does not work the other way around: decreasing neurogenesis or increasing neurodegeneration does not necessarily lead to depression (Santarelli, et al., 2003). Although neurogenesis may be associated with the antidepressant response, it is not clear that neurodegeneration is the cause of depression to begin with. From the above discussion of the vulnerability hypothesis, there is evidence that reduced neuronal volume may result from atypical neurodevelopment, as opposed to neurodegeneration.

An alternative explanation for the efficacy of antidepressants is its effects on neuroplasticity. The brain is a learning machine that has evolved to adapt to its environment, and neuroplasticity is crucial for survival as it allows for neural structures to adapt to perturbations of allostatic load. Plasticity of the nervous system is known to be more labile during development than adulthood, however, it is hypothesized that antidepressant treatments may work by increasing neuroplasticity in adulthood. In fact, there is evidence that antidepressants can increase neuroplasticity, in general. For example, fluoxetine has been shown to restore ocular dominance plasticity in the adult visual cortex and even visual function in previously amblyopic rats (Vetencourt, et al., 2008). These changes were also coupled with increased expression of BDNF. Another landmark study showed that genetic manipulation of the timing of BDNF expression also affects the timing of critical periods (Berardi, Pizzorusso, & Maffei, 2000). Therefore, BDNF plays a causal role in activating critical periods, precisely controlling the onset and offset of plasticity.

In light of the evidence, the neurogenesis final common pathway theory is not supported. However, knowing that the final common pathway is not chemically-based nor neurogenesis-dependent, researchers began to test hypotheses based on brain structure and networks (Castrén, 2005). This network approach views the brain from the perspective of information processing theory, where information is encoded in its structure and function, as opposed to localized regions (Stam & Reijneveld, 2007). In other words, it's not the regions that are activated, but the pattern of activation and connectivity between regions that determine a healthy functional brain network. In addition, the fact that grey matter volume is composed mostly of supporting glia, dendritic branches, and synapses, rather than neurons themselves, suggests that reduced volume may represent altered connectivity, or complexity of the system, rather than reduced function, *per se* (Castrén, 2005). These structural changes may also allow the condition to persist, in contrast to normal episodes of sadness which are not accompanied by changes to neural structure (Henn & Vollmayr, 2004). These structural changes may explain the lag in antidepressant response; Antidepressants then induce neuroplasticity in an activity-dependent manner, targeting those structures that have been compromised.

Mayberg (2000) proposed that the brain regions that are disrupted in depression are those subserving attentional control networks and those subserving emotion regulation, based on the observation that executive function and sadness are often antagonistic to one another. These reciprocal responses are observed in both clinical

depression and normal sadness (Mayberg, et al., 1999). Several studies have shown consistent patterns of changes in activation and metabolism within these networks, specifically, a synchronized pattern of hypoactivation of DLPFC and inferior parietal cortex, coupled with hyperactive ventral mPFC, amygdala, and subgenual ACC (Mayberg, Brannan, Tekell, Silva, Mahurin, McGinnis, & Jerabek, 2000; Drevets, Bogers, & Raichle, 2002). The antidepressant response shows the reverse pattern, where after treatment remitted patients recruit the prefrontal cortex to a greater extent than healthy controls, indicating a greater effort to down-regulate emotion (Kerestes, et al., 2011). In fact, reduced prefrontal cortex activity is found to be in common with three types of depression: unipolar, bipolar, and depression co-morbid with obsessive-compulsive disorder (OCD), but not OCD in the absence of depression (Baxter, et al., 1999).

Other network hypotheses have been proposed, each encompassing various symptom clusters characteristic of depression. One of the most prominent symptoms seen in depression, and one that must be present in order to diagnose the disorder, is anhedonia, or reduced motivation to approach once pleasurable activities. Further evidence to support the concept that symptoms arise as a result of dysfunctional networks, rather than isolated neural structures, is a study showing that depressed patients are capable of experiencing positive emotion as evidenced by activation of ventral striatum circuitry, but this activity is not sustained (Heller, et al., 2009). Thus, compared to healthy controls, responses to positive stimuli seem to be inhibited in patients with depression. The inhibiting factor has been hypothesized to be stress, such

that there is an antagonistic dynamic between positive motivation networks and negative stress networks (Stone, Lin, & Quartermain, 2009). Another network that is disrupted in depression is the default-mode network (Broyd, et al., 2009). It has been associated with the symptoms of rumination and over-general memory (Lemogne, et al., 2009; Zhu, et al., 2012). These studies support the hypothesis that depression is associated with altered information processing in specific brain networks, which may be ameliorated by the effects of antidepressants by changing morphology and connectivity. Thus, the network hypothesis seems to represent a very likely candidate of the final common pathway.

Chapter 3

Changes in cortical thickness across the lifespan in major depressive disorder

Wanda Truong¹
Luciano Minuzzi^{2,3}
Claudio N. Soares^{2,3}
Benicio N. Frey^{2,3}
Glenda M. MacQueen⁴
Geoffrey B.C. Hall⁵

¹McMaster Integrative Neuroscience Discovery and Study Program (MiNDS), McMaster University, Hamilton ON

²Mood Disorders Program, St. Joseph's Healthcare, Hamilton ON

³Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton ON

⁴Department of Psychiatry, Hotchkiss Brain Institute, University of Calgary, Calgary AB

⁵Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton ON

Abstract

Background: Findings in the clinical literature are suggestive of differences in the neurobiological mechanisms underlying the development of major depressive disorder (MDD), depending on the age of first onset. The aim of this study is to compare patients who differ in their age-of-onset, while controlling for duration of illness, and number of depressive episodes. By directly comparing early-onset (EOD) and late-onset (LOD) patients, we test whether age-of-onset is associated with changes in the extent or spatial pattern of cortical thinning.

Methods: Cross-sectional comparison of regional differences in cortical thickness in EOD vs. LOD. Age of MDD onset was determined based on retrospective self-reporting of having experienced a first episode of depression prior to the age of 25.

Results: Thinning in the dorsal-lateral prefrontal (DLPFC) cortex, pre- and post-central gyrus, and the lingual gyrus were found in EOD compared to age-matched healthy controls. The LOD cohort also exhibited thinning in the DLPFC, however, the extent of thinning was more localized compared to EOD. In linear regression models controlling for number of depressed episodes, duration of illness, depression severity, and sex, significant differences were found between EOD and LOD in the bilateral posterior cingulate and parahippocampal gyri, and right precuneus, lingual, and fusiform gyri.

Conclusions: Depression onset in early life is associated with greater disturbances in cortical thickness than LOD, even when illness duration and other factors are

considered. These results provide novel insights into vulnerability and how development of depression is differentially affected by age.

Introduction

Many imaging studies of major depressive disorder (MDD) employ cross-sectional designs that do not control for factors such as age-of-onset, duration of illness, and number of depressive episodes. There is growing evidence, however, suggesting that the neurobiological mechanisms underlying the development of MDD may differ depending on the age of first onset. Clinical studies show that early- (EOD) and late-onset depression (LOD) may differ in their genetic origins, symptomatology, course, and prognosis (Zisook, et al., 2004; Korten, Comijs, Lamers & Penninx, 2012; Gollan, Rafferty, Gortner, & Dobson, 2005). EOD is associated with more suicide attempts, sadness, irritability, neuroticism, childhood-onset anxiety disorders, and atypical symptoms, compared to LOD (Zisook, et al., 2004; Korten, Comijs, Lamers & Penninx, 2012). Several studies have indicated that patients with EOD have poor outcomes, including poor response to antidepressant treatment, greater illness severity, higher relapse rate (Kemp, Gordon, Rush & Williams, 2008; Heim, Plotsky & Nemeroff, 2004; Dekker, Ferdinand, van Lang, Bongers, van der Ende, & Verhulst, 2007), and greater duration of illness, after adjusting for current age (Zisook, et al., 2004).

A consistent finding in the literature that separates the clinical profile of EOD from LOD is a greater prevalence of family history in EOD patients (Peterson et al., 2009; Williamson, Birmaher, Axelson, Ryan, Dahl, 2004; Weissman, Wickramaratne, Nomura, Warner, Verdeli, Pilowsky, & Grillon, 2004; Kendler et al., 2001). A longitudinal study (Weissman, Wickramaratne, Nomura, Warner, Verdeli, Pilowsky, & Grillon, 2004), spanning three generations found an effect of familial loading. Furthermore, there

seems to be a trend toward decreasing age-of-onset with each successive birth cohort, with the more recent generations experiencing depression at a younger and younger age (Lavori, Warshaw, Klerman, Mueller, Leon, Rice, & Akiskal, 1993). Specifically, an epidemiological study found that patients with a first-onset of depression before the age of 25 were more likely to have a family history of depression than LOD patients (Kendler et al., 2001).

Less work has been done to explore neurobiological differences between patients with EOD and LOD. One study of cortical gyrification in bipolar disorder (BP), however, has shown that patterns of cortical folding that differentiated between early- (before age 25 years), intermediate- (age 25-45 years), and late-onset (after age 45) patients (Pentilla et al., 2009). This work demonstrates that mood disorders can have a differential impact on the brain depending on the neurodevelopmental stage at which an illness has its first-onset. Increasingly, both BP and MDD are recognized as neurodevelopmental disorders (Paus, Keshavan, & Giedd, 2010), with the identification of prodromal symptoms and the recognition of onsets in childhood and early adolescence (Kovacs & Lopez-Duran, 2010).

Structural imaging studies in MDD show alterations to cortical structures (Lorenzetti, Allen, Fornito, & Yucel, 2009), but whether these changes reflect neurodevelopmental influences or arise with increasing duration of illness or number of depressive episodes remains unclear. To date, there are 7 studies of cortical thickness that have included patients with MDD. Findings across age groups vary widely in

reported brain regions, with inconsistencies found within regions. Table 1 presents a summary of this literature. In general, early-life MDD and family history of MDD seem to be associated with the largest differences in cortical thickness and affecting a larger expanse of the cerebral cortex (Fallucca, et al., 2011; Peterson, et al., 2009).

Furthermore, many of the areas that are being reported in these groups do not fit the expected cortico-limbic regions widely reported in the functional and volumetric literature. For example, cortical thinning in right lateral parietal cortex was found to mediate familial risk for depression via poor performance on tasks assessing attention for social and emotional stimuli (Peterson et al., 2009).

Findings in late-life MDD, on the other hand, are less consistent. One study found no differences in a sample of late-onset patients compared to healthy, age-matched controls, and no effect of illness duration, number of episodes, or depression severity (Koolschijn, et al., 2010). These findings may support a separate pathophysiological mechanism of late-life MDD, possibly involving white-matter (Sheline, et al., 2010) or subcortical abnormalities, such as the amygdala (Burke, McQuoid, Payne, Steffens, Krishnan, & Taylor, 2011), rather than changes in cortical structure. In contrast, early-life MDD and family history of MDD both involve extensive changes to the cortical mantle, possibly reflecting developmental processes, as these changes appear early in life.

Given the clinical and qualitative distinctions seen between EOD and LOD, and the known differences in the neurodevelopmental stage of the brain at the time of

depression-onset, it is possible that brain structure may be differentially affected in EOD and LOD. The heterogeneity of the clinical profile of MDD suggests that there must be many factors involved in its etiology and many pathways by which the brain reaches the final outcome of depression. Thus, the aim of the current cross-sectional study is to determine whether age-of-onset will be associated with differences in the extent or spatial pattern of cortical thinning, independent of duration of illness and number of depressive episodes, by comparing cortical thickness in EOD and LOD patients, and healthy controls (HC).

We chose to measure cortical thickness as it is a sensitive (Lerch & Evans, 2005) and specific (Lerch, Pruessner, Zijdenbos, Collins, Teipel, Hampel, & Evans, 2008) measure of brain structure, is a candidate endophenotype of MDD (Peterson & Weissman, 2011; Gottesman, 2003), has been associated with connectivity (Jiao, Chen, Ke, Chu, Lu, & Herskovits, 2010), and has a neurobiological interpretation as a measure of the cortical column (Singh, et al., 2006; Mangin, Jouvent, & Cachia, 2010). In addition, cortical thickness has been shown to be affected in many other neuropsychiatric illnesses, including Alzheimer's disease (Singh, Chertkow, Lerch, Evans, Dorr, & Kabani, 2006) Schizophrenia (Van Haren, et al., 2011) and Bipolar Disorder (Lyyo, et al., 2006). We hypothesized that localized regions of cortical thinning would be found in the dorsal lateral prefrontal cortex, medial prefrontal cortex, anterior, and posterior cingulate cortex, based on current models on the pathophysiology of MDD (Mayberg, Brannan, Tekell, Silva, Mahurin, McGinnis, & Jerabek, 2000; Drevets, Bogers, & Raichle, 2002).

Methods and Materials

Participants

Participants were recruited through the Mood Disorders Program and the Women's Health Concern Clinic at St. Joseph's Hospital in Hamilton, Ontario, Canada, through studies that were approved by the Research Ethics Board of St. Joseph's Healthcare Hamilton. All subjects gave informed consent after a full explanation of the study protocol. Exclusion criteria were as follows: history of head injury, neurological illness, alcohol or substance abuse, and previous history of electroconvulsive therapy or transcranial magnetic stimulation within the last two years. Healthy controls were recruited from the community, were not taking any medication, and had no current symptoms of a mental health disorder. A psychiatrist confirmed a primary diagnosis of unipolar MDD using the structured clinical interview for the DSM-IV (SCID; American Psychiatric Association, 1994).

Definitions of EOD in the literature have been inconsistent in their age cut-offs. EOD may include childhood-onset and adolescent-onset depression, however, with a lack of consensus on the upper age-limit, a comparison of studies will result in inconsistent findings. It is important that a biologically-based criteria for defining the age-cut-off between EOD and LOD is used; thus in order to operationalize early- and late-onset depression, we used a first-onset cut-off of 25 years, which is associated with family history of MDD (Kendler, et al., 2005), and has been used as a cutoff in previous

research on mood disorders (Bellivier, et al., 2003) and genetic association studies (Massat, et al., 2005). The average age at-testing in the EOD group was $M = 25.11$, $SD = 10.21$, and $M = 49.59$, $SD = 8.12$ in the LOD group. Data on family history, medication, scores on depression severity rating scales, co-morbid diagnoses, and number of depressive episodes were collected and archived in comprehensive patient databases. Table 2 outlines the demographic and clinical variables between EOD and LOD patients. Figure 1 shows the age-of-onset distribution of the entire sample.

Measures

The 21-item Beck Depression Inventory (BDI-II) and the 17-item Hamilton Depression Rating Scale (HAM-D) were collected from both the patients and control groups. For some participants, only BDI-II scores were available. In order for comparison, we converted the BDI-II scores into the scale of the HAM-D (the most common instrument used), using the following formula (Thorlund, Walter, Johnston, Furukawa, & Guyatt, 2011):

$$M_A = (M_B - L_B) (R_A/R_B) + L_A$$

$$SD_A = SD_B (R_A/R_B) + L_A$$

Where A = HAM-D; B = BDI-II; M = mean estimate; SD = standard deviation; L = lower range of instrument; R = range for instruments. Raw scores were converted into

categorical variables, based on the scales of the respective instruments, in the final models for comparison.

Imaging parameters

T1-weighted anatomical brain scans were acquired in the sagittal orientation on a 3 Tesla GE short-bore MRI system (General Electric Healthcare, Milwaukee, WI) and a standard quadrature head coil. The scan parameters were: 3D-FSPGR scan; TR/TE 18/3.4 ms, flip angle = 20°, FOV = 240 mm, slice thickness = 1.2 mm, matrix size = 512 × 256).

Study Procedure

Figure 2 shows a flowchart outlining the procedure used to exclude scans. Three hundred and ninety-four MRI scans were collected between 2005 - 2011. One hundred and eighty-two scans were excluded due to being acquired from a 1.5 Tesla scanner. Stage 1 quality control involved assessing scans for excessive movement, wrap artifact, or gross anatomical abnormalities. Five subjects were missing both HAM-D and BDI-II scores and/or age-of-onset information. One hundred and forty-one scans were processed on the Corticometric Iterative Vertex-based Estimation of Thickness (CIVET) pipeline (described below). Twenty-eight scans failed on the pipeline, resulting in a total sample size of 113 scans. Stage 2 quality control involved assessing for precision of

tissue classification and image registration, using a cut-off of 15% tissue outside skull mask.

Cortical thickness

CIVET is a pipeline, or a collection of scripts that calls upon a number of tools to automate and process an MRI image in sequence (CBRAIN project, <https://cbrain.mcgill.ca/>). Before processing scans through the CIVET pipeline (Kabani, Le Goualher, & MacDonald, 2001), images were pre-processed using the Montreal Neurological Institute (MNI) imaging tools to reduce noise and improve registration. First, images were cropped to fit the skull in the field of view. This was done in order to remove excess noise from the image background. Next, an intensity threshold was applied to the image background to remove any voxels with intensity less than 100.

Briefly, the steps of the CIVET pipeline start with non-uniformity correction by applying an N3 distance of 200, tricubic interpolation, standardization to stereotaxic space (ICBM 152 dataset average brain in MNI-Talairach space), brain masking, classification into 3 tissue classes (cerebral spinal fluid, grey-matter, white-matter), and surface extraction. The inner and outer cortical surfaces were extracted using the Constrained Laplacian Anatomic Segmentation using Proximity (CLASP) (MacDonald et al., 2000; Kim et al., 2005) algorithm. Cortical thickness was compared across subjects following surface-based expansion and alignment of surface meshes.

Statistical analysis

Statistics Package for the Social Sciences, version 20 (SPSS, Chicago, IL) was used to compare groups on demographic and clinical variables. One-way analysis of variance (ANOVA) was used to compare means across groups for continuous variables, chi-square tests for categorical variables, and Student's t-test for two independent samples, significance level at $p < 0.05$. Pearson correlations were conducted to compare the correlation between clinical and demographic variables with cortical thickness.

SurfStat (Worsley, et al., 2009) was used to analyze cortical thickness data in Matlab (R2010b). Output of the CIVET pipeline results in a 2×40971 matrix of vertices per subject. A between-group analysis of covariance (ANCOVA) of cortical thickness, while controlling for the effects of age, sex, and depression scores was conducted. Within-group ANCOVA controlled for the effects of number of depressive episodes (McKinnon, Yucel, Nazarov, & MacQueen, 2009), duration of illness (Sheline, Sanghavi, Mintun, & Gado, 1999), scores on the measures of depression severity (Chen, et al., 2007), and sex (Sowell, et al., 2007). The interaction between age-of-onset (EOD, LOD) and group (MDD, HC) was examined. These factors have been shown to impact brain morphology in MDD. T-tests were used to test the significance of adjusted beta weights and an F-test was conducted to test the significance of the nested general linear model (GLM) against a null model. Results are displayed as t-maps across the cerebral surface.

Correction for multiple comparisons used random field theory (RFT) using a 20 mm blurring kernel (Taylor & Worsley, 2007). Whole-brain analyses were first conducted to find significant vertices at a significance level of $p < 0.05$, RFT corrected. Next, *a priori* ROI analyses were conducted, uncorrected $p < 0.001$. ROI areas, defined in Talairach space using *Talairach Client*, included the clusters that compose the dorsal lateral prefrontal cortex (DLPFC), medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC) and the posterior cingulate cortex (PCC) (Mayberg, Brannan, Tekell, Silva, Mahurin, McGinnis, & Jerabek, 2000; Drevets, Bogers, & Raichle, 2002). ROI analyses are known to result in better prediction accuracy than whole-brain exploratory analyses (Chu et al, 2012) and minimizes penalty for multiple comparisons by averaging the significant vertices that make up the ROI. The cluster threshold was set at $t = 3.17$, $p < 0.001$, uncorrected. Exploratory results were also reported at a significance level of $p < 0.001$, uncorrected. Effect sizes are reported as the standardized mean differences (SMD) between groups.

Results

Between-group contrast: EOD - HC

Figure 3 shows that compared to healthy controls, EOD patients had significantly thinner cortex in the DLPFC (composed of the superior frontal, middle frontal, and inferior frontal gyri; SMD = 1.42), pre- and post-central gyri (SMD = 1.61), and the lingual gyrus (SMD = 1.15) (Table 3).

Between-group contrast: LOD - HC

No significant results at the whole-brain level were found in the between-group comparison of LOD patients and controls, however, ROI analyses revealed a trend towards thinner DLPFC ($t = 4.35$, $p = 0.06$). The spatial expanses of the differences were much less compared to the EOD group (Figure 4).

EOD vs LOD

Directly comparing the EOD patients with the LOD patients revealed significant differences in several areas (Figure 4); The left and right posterior cingulate gyrus, right lingual, fusiform and precuneus were significantly thicker in the EOD group compared to LOD. Areas that were thinner in the EOD group included the left and right parahippocampal gyri. There were no significant differences in DLPFC (Table 4). The mean thickness (mm) in the DLPFC in the LOD patients ($M = 2.80$, $SD = 0.27$) did not differ significantly from thickness in the EOD group ($M = 2.92$, $SD = 0.35$), $t=1.30$, $p=0.12$. These results remain significant after controlling for the effects of duration of illness, number of depressive episodes, and depression severity (Figure 5).

Within-group: correlations with clinical variables

There was a positive correlation between the number of depressed episodes and duration of illness ($r = 0.47$, $p < 0.001$). No correlations were found between age and number of depressive episodes ($r = 0.25$, $p = 0.09$), or age and duration of illness ($r = 0.15$, $p = 0.12$).

Thickness in the posterior cingulate cortex was significantly correlated with depression scores (HAM-D), after controlling for age. Upon further analysis, it was identified that for the MDD group, thickness of the posterior cingulate was positively correlated with scores on the HAM-D ($r = 0.42$, $p < 0.001$) and negatively correlated with age ($r = -0.67$, $p < 0.001$, Figure 6). Otherwise, thickness in this area tends to decrease with increasing age, as do most areas of the cortex (Sowell, et al., 2003). Cortical thickness in the other ROIs did not correlate with depression severity, duration of illness, or number of episodes.

Discussion

After separating the entire sample into early- and late-onset groups, significant differences were apparent in the EOD group compared to HCs, with patients exhibiting thinner cortex in the pre- and post-central gyri, DLPFC (composed of the superior frontal, middle frontal, and inferior frontal gyri), and the lingual gyrus. The contrast between LOD and HCs revealed a trend towards differences in the DLPFC. However, directly comparing EOD and LOD patients did not reveal significant differences in the DLPFC, suggesting that the mean cortical thickness of DLPFC is comparable across MDD groups. Thickness in this region of the cortex is known to increase until the mid-20s when it reaches its peak thickness, and continually decreases after age 30 (Sowell, et al., 2003). LOD and age-matched healthy controls differed in this region, however, the spatial expanse of the cortical thinning was more widespread in the EOD

group compared to the LOD group.

These results suggest that although older individuals may already exhibit thinning in the DLPFC due to aging, the impact of depression may be to accelerate the thinning process in this region. Depression at an earlier age, on the other hand, may be driven by disrupted neurodevelopment with the resultant thickness in this region being comparable to that seen in a healthy aged adult. This may suggest that thinning of the DLPFC does not necessarily translate to depression in older adults, but thinning in this region does impact significantly on brains that are still developing. These results are consistent with a study examining a comparable group of late-onset MDD patients ($n = 28$), which reported no differences in cortical thickness compared to age-matched healthy controls (Koolschijn et al., 2010). It should be noted, however, that while another recent study by Jarnum and colleagues (2011) ($n = 23$) did not report cortical thinning in the DLPFC, they did identify thinning in other regions, including the orbitofrontal cortex, superior temporal gyrus, insular cortex and posterior cingulate cortex.

The differences between EOD and HCs were consistent with earlier studies in childhood-onset depression (Fallucca, et al., 2011) and at-risk individuals (Peterson, et al., 2009). In both of these studies, differences in cortical thickness were driven by family history. It is possible that the results of the current study may also be driven by family history, as the majority of (17 out of 28) patients in our study fell into this category.

Comparing the EOD patients with the LOD patients showed increased thickness

for EOD patients in the left and right posterior cingulate cortex, right precuneus, fusiform and lingual gyri. Increased thickness in the PCC in EOD may be due to age, as this area is also thicker in young healthy controls compared to older healthy controls (Grieve, Korgaonkar, Clark, & Williams, 2011). However, we found a positive association between thickness in this region and depression severity, as measured by scores on the HAM-D. HAM-D scores between the early and late depressed patients did not differ significantly ($t = 0.26$, *ns*). Peterson and colleagues (2009) found thicker posterior cingulate cortex in subjects at familial risk of depression compared to healthy subjects with no family history of psychiatric illness.

One hypothesis to explain the differences in cortical thickness across studies may be genetic factors. In a recent study, only those patients with both the met version of the BDNF gene and the short allele of the 5HTTLPR gene had increased activation in both the posterior and anterior cingulate cortex in response to sad stimuli (Wang, Ashley-Koch, Steffens, Krishnan & Taylor, 2012). Patients with this combination also had the highest depression and rumination scores in previous studies (*e.g.* Clasen et al. 2011). The posterior cingulate cortex was also positively correlated with scores on the HAM-D in the current study. Thus, it is possible that these were patients with the met-BDNF x short 5HTTLPR genes, which might have a role in mediating the development of cortical thickness in this area.

Cortical networks affected by changes in cortical thickness

The finding of thinning in DLPFC in depressed patients corroborates a large body of existing evidence implicating a key role of the DLPFC in the pathophysiology of depression--specifically the cortico-limbic network hypothesis (Drevets, Price, & Furey, 2008). Mayberg (2000) proposed that the brain regions that are disrupted in depression are those subserving attentional control networks and emotion regulation networks, which are often antagonistic to one another. Several studies have shown consistent patterns of changes in activation and metabolism within these networks, specifically, a synchronized pattern of hypoactivation of DLPFC and inferior parietal cortex, coupled with hyperactive ventral mPFC, amygdala, and subgenual ACC (Mayberg, Brannan, Tekell, Silva, Mahurin, McGinnis, & Jerabek, 2000; Drevets, Bogers, & Raichle, 2002). The antidepressant response shows the reverse pattern, where after treatment remitted patients recruit the prefrontal cortex to a greater extent than healthy controls, indicating a greater effort to down-regulate emotion (Kerestes, et al., 2011). In fact, reduced prefrontal cortex activity is found to be in common in three types of depression: unipolar, bipolar, and depression co-morbid with obsessive-compulsive disorder (OCD) (Baxter, et al., 1999).

The DLPFC is also implicated in task-positive, dorsal attention networks, which are anti-correlated with the default mode network (DMN) (Broyd, et al., 2009). DMN areas that exhibited cortical thickness changes in the present study were the posterior cingulate and the precuneus. Both increased activity and grey-matter density in the posterior cingulate has been shown to correlate with lapses of attention (Söderqvist, McNab, Peyrard-Janvid, Matsson, Humphreys, Kere & Klingberg, 2010).

Adolescents at-risk for depression display increased negative self-focus and maladaptive rumination, which are proximal predictors of depression onset (Jacobs, Reinecke, Gollan, & Kane, 2008), and also share neural correlates with the DMN (Lemogne, et al., 2009; Zhu, et al., 2012).

Uniquely, the present study found significant differences in regions known to be involved in emotional face-processing networks (Fusar-Poli, et al., 2009), namely the fusiform gyrus, lingual gyrus, and the parahippocampus. This finding is in line with several studies investigating emotional face-processing in MDD (e.g. Jacobs, et al., 2011) showing that whereas healthy participants interpret neutral faces as happy, depressed participants consistently display a negativity bias, interpreting neutral faces as sad (Gollan, Pane, & McCloskey, 2008).

Possible differences in etiological mechanisms

As a working model, the vulnerability hypothesis is able to explain the phenomena of EOD. It posits that the combination of genetic and environmental risk factors play an important role in sensitizing the brain to future stressors, influencing neurodevelopment of the HPA-axis and emotion regulation circuitries (Lupien, McEwen, Gunnar, & Heim, 2009). Support for this view is evidence from studies of adolescents with a family history of depression, longitudinal studies on the course of residual symptoms, and symptoms that precede an episode of depression. These studies have elucidated a depressive “cognitive profile”, consisting of cognitive tendencies to

selectively process and store negative stimuli (Hamilton & Gotlib, 2004). For example, one study found that hyperactivity in the amygdala during the encoding of emotionally-neutral stimuli is a trait response in MDD, as it is present during a depressive episode and during remission (van Eijndhoven, van Wingen, Fernández, Rijpkema, Verkes, Buitelaar, & Tendolkar, 2011). There are also abnormalities in information processing. Poor performance on tasks assessing attention for social and emotional stimuli was correlated with greater depression severity and predicted life-time rates of MDD in a sample with a family history of MDD (Peterson et al., 2009).

There is also evidence that reduced cortical thickness in EOD patients may be a result of atypical neurodevelopment (Gatt, Nemeroff, Schofield, Paul, Clark, Gordon, & Williams, 2010), as opposed to neurodegeneration (Sapolsky, Krey, & McEwen, 2002). Periods of development (*i.e.* infancy and early childhood) and decline (*i.e.* old age) seem to be particularly sensitive time frames to the effects of stress, as they are periods characterized by dynamic change and increased neuroplasticity (Lupien, et al., 2009). In contrast, the mechanisms behind cortical alterations occurring in older age may not involve actual loss of neurons, as was once widely believed (Wickelgren, 1996). Rather the mechanism seems to be a combination of neuronal shrinkage, reduced neurogenesis, and changes to myelination and dendritic branching, while generally preserving the neuronal cell count (Terry, DeTeresa, & Hansen, 1987; von Bohlen und Halbach, 2010). This is in contrast to animal work showing that stress during development results in reduced neuronal cell counts in prefrontal regions, which may be mediated either by reduced neurogenesis or increased apoptosis (Mychasiuk, Gibb, &

Kolb, 2012). Evidence that stress attenuates neurogenesis in adult hippocampus suggest that opportunities to develop depression in adulthood may arise due to plasticity of the brain (Duman & Monteggia, 2006).

Limitations

The present study of patients in a current episode of depression was limited by its cross-sectional design. Thus, inferences on trajectories of change within an individual cannot be made from the present data. In addition, the sample was divided into 4 subgroups, which decreased statistical power in each group. However, effect sizes were large and sample sizes were comparable to those seen in the literature. Another limitation is that not all patients were antidepressant-naive, which is known to influence cellular changes in the cortex (Duman & Monteggia, 2006). Directions for future study should include longitudinal designs following EOD patients, and should test interactions between genotype and age-of-onset.

Conclusions

While clinical research points to differences in symptomatology, course, and prognosis between early (EOD) and late-onset depression (LOD), our understanding of the importance of age of onset on differences in brain morphology is less clear. This study showed that depression onset in early-life may be associated with greater disruptions in cortical thickness than late-life onset, even when illness duration and

other factors are considered. However, when presenting with a current episode of depression, the age of depression onset may provide useful clinical information regarding prognosis or treatment strategy. Few studies have included age-of-onset in their analyses which may account for some of the heterogeneous results seen in cortical thickness studies of MDD. This is the first study to investigate the influence of age-of-onset on cortical thickness in MDD, with results possibly reflecting atypical neurodevelopment in EOD patients.

Figure 1: Distribution of age-of-onset in the sample

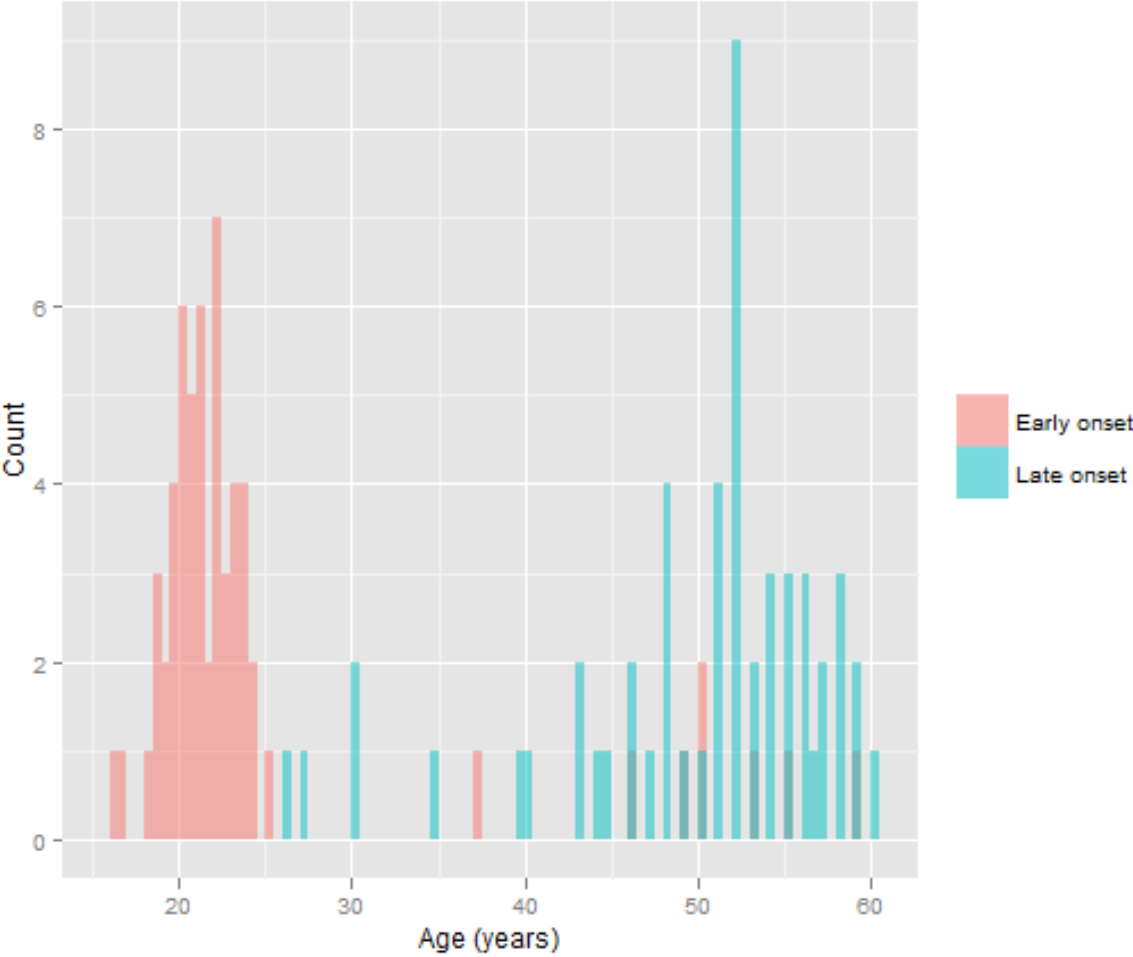
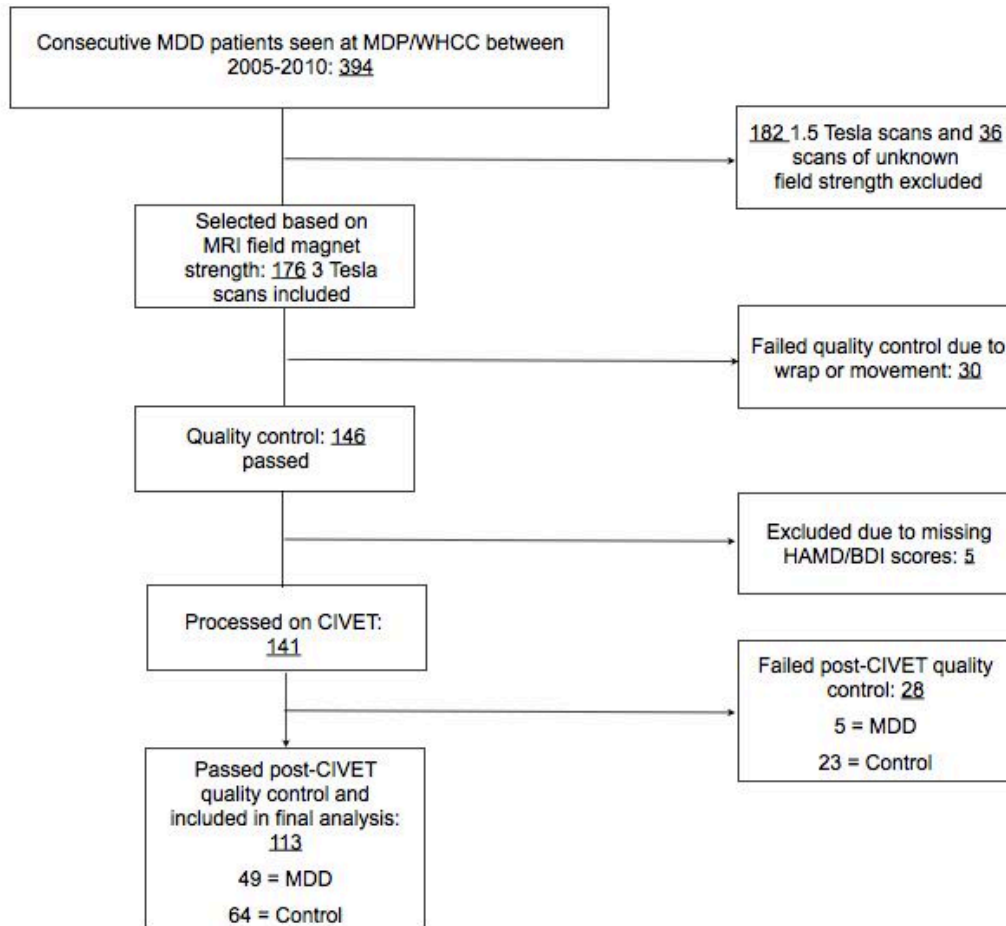


Figure 2: Flowchart outlining procedure used to exclude scans

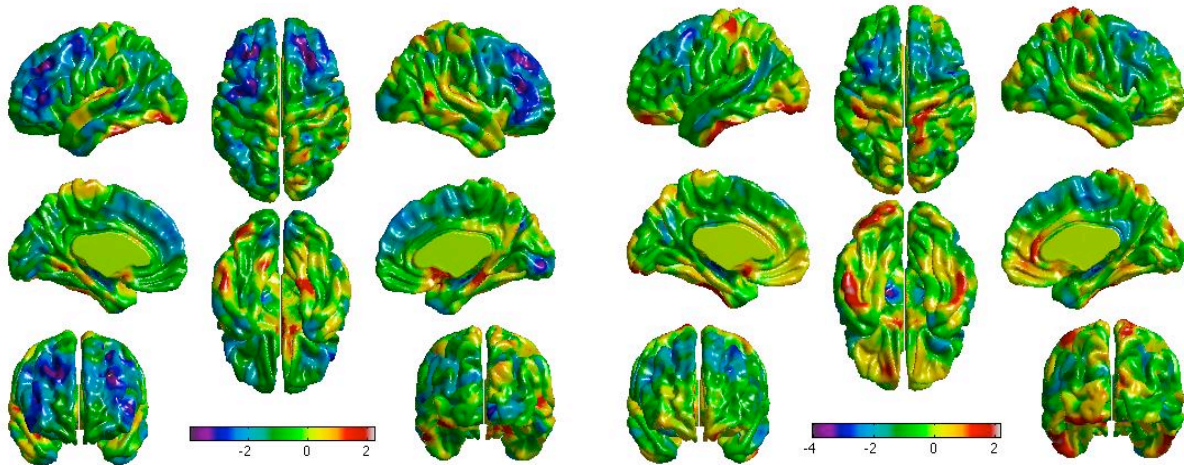


MPD = Mood Disorders Program
 WHCC = Women's Health Concerns Clinic
 QC = Quality control
 HAMD = Hamilton Rating Scale for Depression
 BDI = Beck Depression Inventory
 CIVET = Corticometric Iterative Vertex-based Estimation of Thickness
 MDD = Major Depressive Disorder

Figure 3: T- map of between-group comparisons in the early-onset group (A) and the late-onset group (B).

A. EOD - HC

B. LOD - HC



The dorsal lateral prefrontal cortex is affected in both the EOD ($t = 3.17$, $p < 0.001$) and LOD groups ($t = 4.35$, $p = 0.058$), however, the spatial extent of cortical thinning is greater in the EOD group.

EOD = Early-onset depression
LOD = Late-onset depression
HC = Healthy control

Figure 4: T-map of between-group comparison of early-onset depression with late-onset depression.

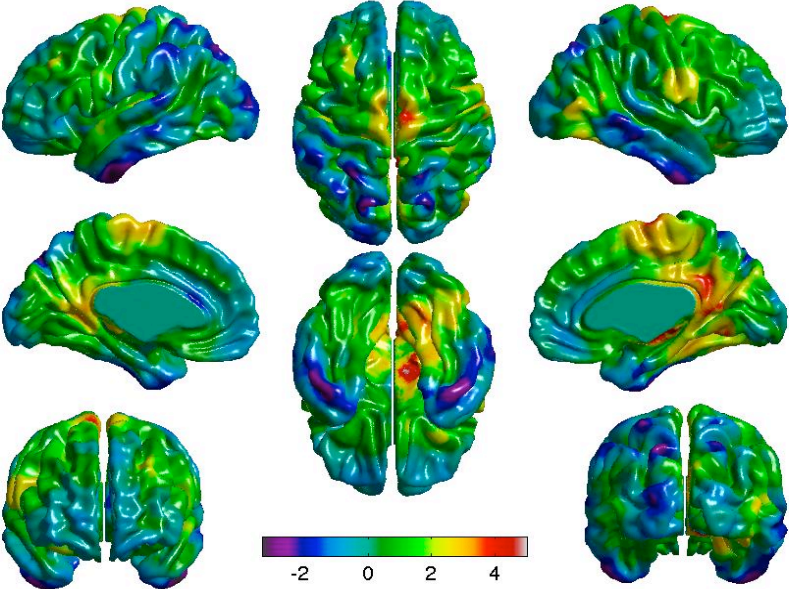
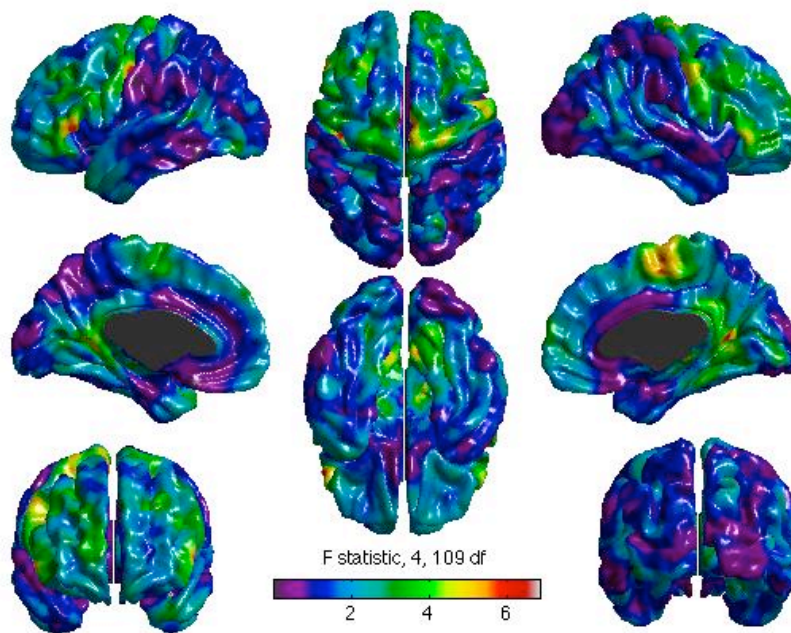


Figure 5: F-map showing interaction between group and age-of-onset.



The colour bar shows the F-statistic with warmer colours indicating areas of the cortex significantly accounted for by the general linear model, consisting of number of depressive episodes, duration of illness, depression severity and sex.

Figure 6: Graph depicting the relationship between thickness in the posterior cingulate cortex, adjusted for age, and scores on the Hamilton Depression Rating Scale (HAM-D).

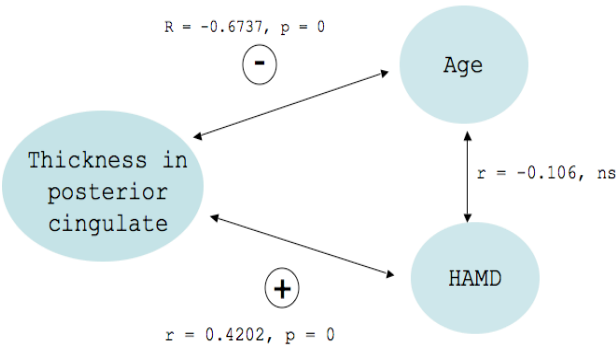
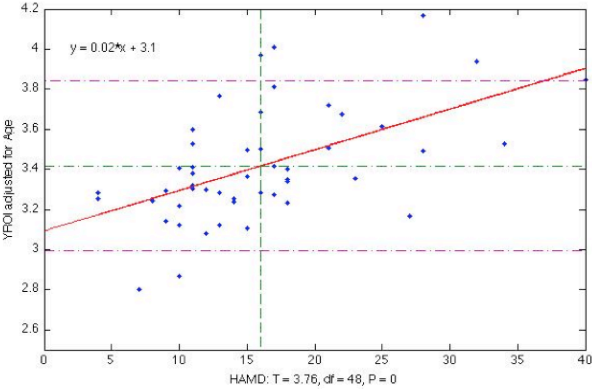


Table 1: Literature review.

Author	Year	Participants	Age mean (SD)	Number of episodes	Duration of illness (months)	Cortical thickness method	Results
Peterson	2009	66 At-risk (12 children, 54 adults), 65 HC (31 children, 34 adults)	Children under 18, adults ranged from 18-54	n/a	n/a	FreeSurfer	Thinning in lateral surface of R hemisphere (inferior and middle frontal gyri, somatosensory, motor cortex, dorsal and inferior parietal, inferior occipital gyrus, posterior temporal); Thickening in subgenual ACC, PCC, medial orbitofrontal cortex
Koolschijn	2010	28 female late-life MDD, 38 HC	64.04 (10.90); average age-of-onset = 33 (9.48)	11.14 (14.12); range 1-49; median = 4	93.50 (17.50)	CLASP	No differences in cortical thickness between groups, no effect of illness duration, severity, or number of episodes
Jarnum	2011	23 MDD, 26 HC	43 (9.9)	2.1(1.8)	not reported	FACE	Baseline: thinner orbitofrontal, superior temporal gyrus, insular cortex between groups; Thinner posterior cingulate in non-remitters than remitters; Follow-up: thinner orbitofrontal at baseline
Fallucca	2011	24 paediatric MDD, 24 OCD, 30 HC	13.96 (2.41)	not reported	24.90(31.32)	FreeSurfer	Regions thinner in depressed vs. controls: R pericalcarine gyrus, R post-central gyrus, R superior parietal gyrus, L supramarginal gyrus; Regions thicker in depressed vs. controls: R and L temporal poles
Colloby	2011	38 late-life MDD, 30 HC	74.1 (6.1); First-onset 51.8 (22.3)	not reported	276.0(258.0)	FreeSurfer	No significant differences in cortical thickness in frontal lobes (ROI) between groups
Kumar	2012	16 minor late-life depression, 16 HC	76.25 (7.54)	1 subject had a previous episode of MDD	12/16 had duration longer than 2 years	FreeSurfer	Thinner R cingulate cortex (isthmus) between groups
Lim	2012	45 late-onset MDD, 47 HC	71.8(4.8)	not reported	15.6(6.0)	FreeSurfer	Thinner rostral ACC, mOFC, DLPFC, superior and middle temporal gyrus, and PCC in MDD compared to HC

Table 2: Demographic data

	HC-Early n = 32 mean (SD)	MDD-Early n = 28 mean (SD)	HC-Late n = 32 mean (SD)	MDD-Late n = 21 mean (SD)	Test statistic	P-value
Age	21.39(1.91)	24.47(9.34)	48.99(8.93)	49.52(8.5)	75.39*	<0.001
Sex (% Female)	100	70	87.5	46	16.77**	0.001
Education (years)	15.81(1.80)	13.87(2.14)	17.30(2.06)	16.67(3.12)	6.94*	<0.001
Episodes	n/a	1.61(0.72)	n/a	3.31(2.66)	3.24†	0.002
Duration (months)	n/a	45.04(48.14)	n/a	102.91(112.75)	2.44†	0.02
HAMD scores§	8.11(5.96)	23.36(11.57)	2.72(2.95)	13.29(5.70)	58.70**	<0.001

HC = Healthy control

MDD = Major depressive disorder

Test statistics:

*F-test

** χ^2 test

†Student's t-test

§BDI-II scores converted to HAM-D scores

Table 3: Quantitative results in the between-group contrast between early-onset patients and age-matched healthy controls.

t	X	Y	Z	Region	BA
4.04*	-42	-2	50	L pre-central	6
3.43**	-24	-42	67	L post-central	5
3.52**	9	-95	-1	R lingual	17
3.75	22	47	37	R superior frontal gyrus	9
3.29	-8	66	19	L superior frontal	10
3.51	48	40	-6	R middle frontal	47
3.32	48	40	-10	R inferior frontal	47
3.25	-48	33	-9	L inferior frontal	47

* Significant at $p < 0.05$, RFT corrected.

** Significant at whole-brain level, $p < 0.001$, uncorrected

§ Significant at the region-of-interest (ROI) level, $p < 0.001$, uncorrected

R = Right hemisphere

L = Left hemisphere

BA = Brodmann area

Table 4: Quantitative results in the between-group contrast between early-onset patients and late-onset patients.

t	X	Y	Z	Region	BA	Direction
3.36	-5	-47	12	L posterior cingulate	29	Thicker in EOD
3.29	2	-42	17	R posterior cingulate	29	Thicker in EOD
3.23	4	-36	35	R cingulate	31	Thicker in EOD
4.10	10	-50	32	R precuneus	31	Thinner in EOD
3.26	-15	-28	-5	L parahippocampal	35	Thinner in EOD
3.24	31	-38	-15	R fusiform	20	Thinner in EOD

Results are significant at the exploratory level, $p < 0.001$, uncorrected

R = Right hemisphere

L = Left hemisphere

BA = Brodmann area

EOD = Early-onset depression

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Chapter 4

Chapter 4: Discussion

4.1 Clinical significance

A World Health Organization (WHO) report predicts that MDD will be the leading cause of disability and premature death in the industrial world by 2020 (Mathers & Loncar, 2006). Current treatments for MDD can be unreliable and time-costly (Mathers & Loncar, 2006), which ultimately translate to economic costs. Timeliness is an important factor in the treatment of an acute depressive episode, which left untreated, often leads to intractability (Keller et al., 1992). Current diagnosis of MDD is based on self-report and clinical assessment of symptoms, tools which are only designed to detect the presence of a depressive episode and are not useful for early risk identification or for guiding appropriate treatment. Furthermore, these methods are not sensitive to the underlying pathophysiology of MDD. Therefore, biologically meaningful assessment tools that reflect the pathophysiology of the disorder are needed.

Given that demographic, clinical, and behavioural measures are not able to discriminate between treatment responders from non-responders (Kemp et al, 2008), it is clear that we need different methods of treating MDD patients. There is accumulating evidence that neuroimaging, specifically magnetic resonance imaging (MRI) can achieve this. MRI is a diagnostic technology that has been available for nearly thirty years, and recently it is believed to provide a way of targeting appropriate treatment, whereas the current treatment options are based on trial-and-error with antidepressants or with non-evidence based therapies (Thase & Rush, 1997).

4.2 Clinical applications: MRI for treatment prediction and prognosis

A growing body of evidence supporting the efficacy of MRI-based diagnostic and prognostic technology has sparked considerable interest in the scientific and clinical communities (Brammer, 2009; Downing, 2009; Bullmore, Fletcher & Jones, 2009; Ecker et al., 2010; Insel, 2009; MacQueen, 2010; Kemp et al, 2008). In order for MRI to play a useful role in the clinical management of MDD it needs to have both specificity (*e.g.* be able to distinguish between unipolar vs. bipolar depression) and sensitivity (*i.e.* allow us to detect the disease before it manifests as an acute depressive episode) for identifying brain-based biomarkers of the disease.

MDD encompasses a wide range of clinical subtypes, each of which may differ in their underlying pathophysiology. There is evidence that MRI combined with machine learning classification is able to diagnose depressive subtypes using brain-based criteria (Nouretdinov et al., 2010; Costafreda, Chu, Ashburner & Fu, 2009). Machine learning involves training a computer to recognize patterns of brain structure or activity that is representative of a population and compares each brain to determine which diagnosis it belongs to (*e.g.* depressed or healthy group, depression or bipolar disorder). It has a sensitivity of 86% of identifying MDD patients based on brain activity (Fu et al., 2008). In addition, it also provides a measure of reliability, or a confidence level, which is useful for assessing the risk of an incorrect diagnosis (Nouretdinov et al., 2010).

Early detection of MDD is crucial for the potential prevention of illness onset in high-risk individuals. Being able to preempt the emergence of the disease is a high priority to health-care policy makers (Canadian Institutes of Health Research, 2005). One longitudinal study that sought to identify biological markers of vulnerability in at-risk individuals with a family history of recurrent and functionally debilitating MDD found significant differences in the thickness of the cerebral cortex between at-risk, healthy, individuals, compared to healthy controls. This result is promising as a potential biomarker of MDD, at least in those with the familial history subtype (Peterson et al., 2010). More studies are needed to determine whether cortical thickness is able to predict treatment responses, and whether this biomarker is consistent across different subtypes of depression.

The ability to accurately match an MDD patient with an appropriate treatment regime would save time and money. Preliminary research with MRI has been successful in identifying brain structures which can serve as clinical predictors of response. For example, pre-treatment activity in the rostral anterior cingulate has been shown to predict eventual response to antidepressants (Mayberg et al., 1997). This result is very well replicated and consistent across multiple studies and methodologies (Davidson, Irwin, Anderle & Kalin, 2003; Mulert et al., 2007; Pizzagalli et al., 2001). A prospective study found that initial hippocampal volume predicted treatment outcome, whereby small initial volumes predicted more relapses than large volumes (Frodl et al., 2008). A meta-analysis reported that decreased hippocampal volume seen in multiple episode patients, but not first episode patients, suggesting that it may be an effect of chronic

illness burden (McKinnon, Yucel, Nazarov, MacQueen, 2009). In addition, machine learning algorithms have also been applied to the prediction of treatment responses. The prediction of a full clinical response to antidepressants has been achieved with 89% accuracy and 86% sensitivity (Costafreda, Chu, Ashburner & Fu, 2009). However, larger randomized controlled studies are needed to determine which treatments are most likely to be effective for a particular subtype of MDD, given the structure or activity of the brain.

4.3 Conclusions

In conclusion, the data presented in this thesis provide evidence for both differences and similarities in patients with early- compared to late-onset depression. Few studies have used age-of-onset as a factor, which may account for some of the heterogeneity and inconsistent results seen in studies of MDD. We found that depression onset in early life is associated with greater disturbances in cortical thickness than LOD, possibly reflecting atypical development. These results provide novel insights into vulnerability and how development of depression is differentially affected by age.

Further research is needed to clarify the influences of genetics and environment, and their combined impact on cortical thickness. In addition, longitudinal studies are needed to confirm whether the trajectory of cortical changes is, indeed, different for depression onset in early life compared to onset in late-life, as is predicted by the

results of this study. Finally, the use of cortical thickness as an endophenotype for depression subtypes is supported by this study.

Finally, within the framework of the three working hypotheses introduced in Chapter 2, how can the existing evidence be synthesized? Earlier studies investigating age of depression onset have implicated vulnerability hypotheses in the etiology of early-onset depression and neurotoxicity in the etiology of late-onset depression. The results of this thesis, however, support a third hypothesis: multiple pathways converge onto a common neural profile of depression. Although different regions are implicated in depression-onset in early life compared to late-life, the similarities seen in the DLPFC is suggestive that this region may be a crucial structure in gate-keeping the cascade of neurobiological changes that may lead to depression onset.

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