

Imaging the human brain on oral contraceptives: A review of structural imaging methods and implications for future research goals



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ABSTRACT

Worldwide over 150 million women use oral contraceptives (OCs), which are the most prescribed form of contraception in both the United States and in European countries. Sex hormones, such as estradiol and progesterone, are important endogenous hormones known for shaping the brain across the life span. Synthetic hormones, which are present in OCs, interfere with the natural hormonal balance by reducing the endogenous hormone levels. Little is known how this affects the brain, especially during the most vulnerable times of brain maturation. Here, we review studies that investigate differences in brain gray and white matter in women using OCs in comparison to naturally cycling women. We focus on two neuroimaging methods used to quantify structural gray and white matter changes, namely structural MRI and diffusion MRI. Finally, we discuss the potential of these imaging techniques to advance knowledge about the effects of OCs on the brain and wellbeing in women.

1. Introduction

Oral contraceptives (OCs) are the most popular form of birth control in the United States and in European countries (King et al., 2021; United Nations, 2019). Worldwide over 150 million women are prescribed OCs (Christin-Maitre, 2013; United Nations, 2019). OCs, commonly known as the “pill,” provide an effective option for contraception and safe family planning (McKenna and Fogelman, 2021; Osayande and Mehulic, 2014). They are increasingly used by adolescent and young women not only to control fertility but for a number of other treatments (Upadhyaya et al., 2017), including symptomatic endometriosis, irregular cycles, heavy menstrual bleeding, menstrual period pain, premenstrual syndrome, and polycystic ovary syndrome (PCOS; Schindler, 2013), as well as so-called life style products to prevent acne or hair loss (Eichenfield et al., 2021; Williams et al., 2021). Hence, the effects of OCs go beyond their original purpose of contraception. However, the rate of women on

OCs has been declining in the past 20 years. In 2010, close to 46% of women insured under a statutory insurance plan in Germany were using prescribed OCs. In 2020, however, it was only 35% (AOK-Bundesverband, 2021). In the Netherlands, in young women under the age of 25 years the use of OCs decreased from 88 to 76% between 2005 and 2017 (Marra et al., 2020). In Spain, the percentage of adolescents and young women using OCs decreased by 4% from 2006 to 2012 (Carrasco-Garrido et al., 2016).

Given the lack of research on this topic, we can only assume that the decline in the use of OCs is likely the result of switching to alternative contraception methods such as hormonal intrauterine devices (IUDs), hormone-free copper-based IUDs (Marra et al., 2020), and/or a rising awareness regarding potential side effects (Rosenberg et al., 1995), such as the risk of venous thrombosis (Khialani et al., 2020), depression, anxiety, and associated suicide attempts (Robakis et al., 2019), with the highest risk in adolescent women (Skovlund et al., 2018). Depression

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and suicidal behavior are strongly associated with alterations throughout the brain (Bani-Fatemi et al., 2018; Korgaonkar et al., 2011). However little is known about the extent OCs affect the brain's function and morphology, although it is known that endogenous sex hormones do shape the brain across the life span in terms of both functional and organizational aspects (Arnold, 2009; Juraska et al., 2013; Phoenix et al., 1959). Thus, investigating the underlying effect of OCs on the brain is important as its use may influence women's health.

In the following chapters, we review the current literature in neuroimaging methods and discuss to what extent neuroimaging can help us understand brain changes across the female menstrual cycle and how OCs might affect the brain's structure. We wrote this review to facilitate the understanding of structural magnetic resonance imaging (sMRI) and diffusion magnetic resonance imaging (dMRI) methods and its application in neuroimaging research on OCs and their effect on the brain. Our idea was to give researchers a hands-on review on the latest and state-of-the-art imaging methods and its applications. First, we provide information about how sex hormones shape the human brain during development and maturation and how OCs containing synthetic hormones suppress the endogenous hormones in the body. Second, we review psychiatric conditions associated with OCs use. Third, we review neuroimaging findings in individuals using OCs. Given the fact, that there are some reviews on functional neuroimaging studies on OCs (e.g. Brønnick et al., 2020; Montoya & Bos, 2017), we focused on imaging methods sensitive to structural changes of gray and white matter, namely sMRI and dMRI. Following this, we introduce neuroimaging methods developed in recent years that are suitable to be applied to OCs-related studies. We conclude with suggestions for future research directions to understand the female brain on oral contraceptives.

2. Sex hormones in association with the female menstrual cycle and the brain

The brain is an endocrine organ strongly tied to the action of neuromodulatory hormones. Since the late 1950s, we know that sex hormones shape the brain during development (Arnold, 2009; Phoenix et al., 1959). The brain represents an important target for endogenous estrogen (estrone, estradiol, and estriol) and progesterone effects, with estradiol being the most influential estrogen in humans (Jeyakumar et al., 2011). Both, estradiol and progesterone, modulate the brain's structure and function through neuroendocrine conditions across a women's life span (Juraska et al., 2013; Rehbein et al., 2021). For example, administration of estradiol increases dendritic growth and synaptogenesis in the neonatal brain (Haraguchi et al., 2012). Moreover, sex hormones influence myelination (Garcia-Segura and Melcangi, 2006), such as administration of progesterone increases myelin formation during brain maturation (Gago et al., 2001) and in the aging brain (Ibanez et al., 2003).

The major source of production of estrogen and progesterone are the ovaries, therefore, both hormones are predominantly present in women (Greenblatt et al., 1976; Orwoll et al., 2006). Both hormones act on the brain: while cells of most brain regions have estrogen and progesterone receptors, an increased distribution of estrogen β mRNA expression is found in the hippocampus, amygdala, claustrum, thalamus, hypothalamus, and the fifth layer of the temporal cortex in *ex vivo* studies (Österlund et al., 2000). Relying on rodent data, the most progesterone receptors are present in the hippocampus, amygdala, cerebellum, hypothalamus, as well as the frontal cortex (Brinton et al., 2008). It should be noted, that there are currently no *in vivo* studies of estrogen and progesterone receptor distributions in the human brain.

Estrogen and progesterone, among other sex hormones, are important for the female menstrual cycle. While the follicle stimulating hormone (FSH) and the luteinizing hormone (LH) cause the maturation and the release of the egg, estrogen and progesterone are involved in thickening and maintaining the uterine lining (Reed and Carr, 2018). During their approximately 28-day menstrual cycle, naturally cycling

women exhibit biphasic variations in serum estradiol with lowest concentrations reported during the early follicular phase, a maximum concentration (first peak) around ovulation and a second, smaller peak during the mid-luteal phase (Soules et al., 1989; Stricker et al., 2006). Estradiol concentrations vary during hormonal transition periods: during pregnancy, estradiol increases up to ninefold but drops dramatically post-partum (Schock et al., 2016) and in menopause (Burger et al., 2002). Similarly to estradiol, progesterone variations are observed in naturally cycling women across the menstrual cycle with lowest concentrations during the early follicular phase and highest concentrations during the mid-luteal phase (Hambridge et al., 2013; Mumford et al., 2013, 2010). As is the case for estradiol, progesterone concentration levels are higher during pregnancy, reaching peak concentrations of up to fourfold (Schock et al., 2016), and dramatically decline in menopause (Burger et al., 2002; Santoro, 2005). Abnormal menstrual cycle patterns throughout adolescence may be a biomarker for potential health concerns in adulthood, such as abnormal blood pressure or heart rate (Diaz et al., 2006; Popat et al., 2008). Irregular menstrual bleeding is also a sign of endometriosis or PCOS, which may result in infertility (Anagnostis et al., 2018; Bachetot, 2016; Macer and Taylor, 2012; Tanbo and Fedorcsak, 2017). Having a healthy menstrual cycle is thus important for the overall health in women of childbearing age. However, the underlying neurobiological mechanisms of how estradiol and progesterone influence the brain across the life span remains mainly unknown. For an overview on brain changes across the natural menstrual cycle phases see Dubol et al. (2021).

OCs alter the natural menstrual cycle and there are two major categories of OCs types: combined OCs containing both ethinylestradiol and progestin, and those containing progestin only OCs. The type of progestin present in different OCs brands varies. The older progestin types are usually referred to as 1st and 2nd generation (e.g. norethindrone, lynestrenol, ethynodiol diacetate, norethisterone, levonorgestrel, and norgestrel), while the newer ones are referred to as 3rd and 4th generation progestins (desogestrel, gestodene, and norgestodene). Older generation progestins are associated with androgenic side effects (Knopp et al., 2001), while newer generation progestins were found to exert anti-androgenic actions (Kuhl, 2012; Sitruk-Ware, 2006). Combined OCs act by suppressing endogenous sex hormone levels of estradiol and progesterone during the active intake phase (Sahlberg et al., 1987). This suggests that women using OCs display lower estradiol and progesterone serum concentrations compared to naturally cycling women (Fleischman et al., 2010). In this line, estradiol and progesterone levels are comparable to the follicular phase of the natural menstrual cycle (Taylor et al., 2020) when sex hormone concentrations are low (Hambridge et al., 2013; Mumford et al., 2013, 2010; Soules et al., 1989; Stricker et al., 2006). During the inactive intake OCs phase, exogenous estradiol rises but is still comparable to the serum levels of the follicular phase of the natural menstrual cycle (De Bondt et al., 2016). Following this, OCs influence and interfere with the natural hormone balance. However, it is not yet fully understood how the synthetic sex hormones introduced by OCs affect the human brain.

Synthetic hormones can have both positive and negative side effects on the human body. Positive side effects are, for instance, treatments of heavy menstrual bleeding, menstrual period pain, PCOS (Schindler, 2013), acne, and hair loss (Eichenfield et al., 2021; Williams et al., 2021). Moreover, exogenous administration of estrogens and progestins acts as a neuroprotective factor after cerebral ischemia and traumatic brain injury in females as well as in males (Brotman et al., 2016; Roof and Hall, 2000). Negative side effects of OCs reflect, for instance, body weight gain (Edelman et al., 2011) or depressive and anxiety like symptoms (Robakis et al., 2019). An overview of mood-related side effects associated with the use of OCs is provided in the next paragraph.

3. Mood-related side effects in women using OCs

Women are approximately twice as likely to be diagnosed with major

depressive disorder (MDD) as men (Seedat et al., 2009). Additionally, fluctuations of ovarian hormones have been associated with depression susceptibility and prevalence in women (Kuehner, 2017). Neuroimaging studies demonstrated abnormalities of the brain in areas such as the prefrontal cortex, cingulate cortex, and subcortical volumes in individuals with MDD (Korgaonkar et al., 2011). Hippocampal volumes in particular are significantly decreased in individuals with depression (Schmaal et al., 2017). Epidemiological data further suggest that hormonal transition periods across the female lifespan, such as puberty, pregnancy, postpartum, and the perimenopause, when levels of estradiol and progesterone either increase or dramatically drop, are periods of increased risk for developing MDD (Zsido et al., 2017). These hormonal transition periods possibly comprises a ‘reproductive subtype’ of depression (Harald and Gordon, 2012).

Moreover, a number of women are particularly susceptible to the subtle hormone fluctuations across the menstrual cycle and develop premenstrual dysphoric disorder (PMDD; Epperson et al., 2012). In an animal study, a sudden withdrawal of progesterone resulted in increased anhedonia and social withdrawal in rats, which represents a robust model for PMDD (Li et al., 2012). Four to 10% of women taking OCs experience depression and anxiety symptoms, irritability, and mood swings (Glick and Bennett, 1981; Kelly et al., 2010). Studies also support mood-related side effects of OCs use (Ross and Kaiser, 2016; Skovlund et al., 2018; Zethraeus et al., 2017; Zettermark et al., 2018), most often occurring in women with a history of depressive symptoms (Bengtsson et al., 2018; Lundin et al., 2017). A trend towards a negativity bias was reported in emotion recognition and reactivity in women using OCs. Furthermore, a trend towards a blunted reward response and a potential dysregulation of the stress response was reported (Lewis et al., 2019). However, some women experience improvements in mood in the premenstrual phase when using OCs (Lundin et al., 2017). In fact, high doses of synthetic progesterone, seem to have an anti-anxiety and sedative effect in postmenopausal and natural cycling women, as well as in men (De Wit et al., 2001; Söderpalm et al., 2004; van Broekhoven et al., 2006). Moreover, women using OCs had a lower prevalence of MDD, anxiety disorder, and panic disorder in the previous year compared to former users and to never users (Cheslack-Postava et al., 2014). It should be noted, that each mental disorder was most common among former users. In summary, use of OCs can likely lead to mood-related side effects, especially in women with previous MDD while in women with symptoms of PMDD, OCs use was reported to have positive effects on mood (Robakis et al., 2019). For reviews and further details on OCs and mood please see Lewis et al. (2019) and Robakis et al. (2019). However, given the inconsistent results on sex hormones in association with mood, it is yet unknown whether these side effects are caused by low levels of endogenous hormones or by the presence of synthetic sex hormones.

Considering the associations between hormonal fluctuations and depression in women using OCs, it would be helpful to understand which individuals are more vulnerable for developing mood specific side effects. To help women make informed choices regarding their contraception method, we first need to understand better the effect of OC use on women’s health and wellbeing.

4. Structural neuroimaging

To investigate the effects of OCs on the brain in humans, we need *in vivo* methods that are also non-invasive. MRI techniques are non-invasive and are well suited to explore brain gray and white matter morphology in individuals in clinical research studies to assess even subtle changes of the brain. In the following sections, we review structural MRI (sMRI) by assessing the brain’s macrostructure in terms of volume of brain regions, cortical thickness, cortical surface area, and gyration in women using OCs and across the female menstrual cycle. Thereafter, we provide an overview of the methods suited to analyze sMRI data and we list the most robust and popular methods. We then

review the methods that have been applied in studies investigating the effect of OCs on the human brain and discuss approaches that are potentially of interest for future studies.

4.1. Findings from structural MRI

4.1.1. Findings on gray matter volumetric changes between naturally cycling women and women on OCs

OC-related studies have reported morphometric abnormalities in whole brain, cortical and subcortical gray and white matter (see Table 1, Fig. 1). Global gray matter (Lisofsky et al., 2016; Pletzer, 2019) and total intracranial volume (Pletzer et al., 2015) were decreased in women using combined OCs when compared to naturally cycling women (combined group of women in the follicular and luteal phase) and to naturally cycling women in the follicular phase.

Cross-sectional studies exploring which of the brain regions might be impacted by the use of OCs report volumetric changes in all lobes (frontal, parietal, occipital, temporal), in subcortical structures and in the cerebellum (see Table 1). Decreases as well as increases of volumes are present. Decreases in gray matter volumes were reported in the bilateral middle and superior frontal gyrus (Pletzer et al., 2015), the right anterior cingulate gyrus, the right lingual gyrus (De Bondt et al., 2016), the left fusiform gyrus (De Bondt et al., 2013a), right putamen (Sharma et al., 2020), left hippocampus (Pletzer, 2019), and right culmen of the cerebellum (De Bondt et al., 2016) in women using OCs when compared to naturally cycling women in both the early follicular and the mid-luteal phase of the menstrual cycle (De Bondt et al., 2016). It should be noted that the volumes of the lingual gyrus and the culmen of the cerebellum were decreased in the inactive intake phase of women using OCs when compared to naturally cycling women in the follicular phase. One of the only longitudinal studies (Lisofsky et al., 2016) reported decreases in the bilateral parahippocampal gyrus and the left amygdala in women using combined OCs. In this study, women were scanned twice: the first scan was acquired during the early follicular or late luteal phase, for the second scan women started using OCs and there the scan was acquired in the inactive OC-intake phase. A closer look to which phase of the natural cycle and phase of OC-intake were compared, is provided in Table 1. Moreover, the brain structures producing estrogen and progesterone, the hypothalamus and pituitary gland, have decreased volumes in women using OCs when compared to naturally cycling women (Chen et al., 2021).

Many studies, though, demonstrated increased gray matter volumes in women using OCs when compared to naturally cycling women. Increased gray matter volumes were reported in various regions across the bilateral prefrontal cortex (De Bondt et al., 2013a; Pletzer et al., 2010; Sharma et al., 2020), the parietal lobe including the bilateral postcentral gyrus, the bilateral supramarginal gyrus, the right inferior parietal gyrus (Pletzer et al., 2010), the occipital lobe (De Bondt et al., 2013a) including the right middle and bilateral inferior occipital lobe (Pletzer et al., 2010), and the bilateral cerebellum (Pletzer et al., 2015, 2010) in women using OCs (active and inactive intake phase) when compared to naturally cycling women in the early follicular, mid-luteal, and luteal phase of the menstrual cycle. In addition, several gray matter volume increases were reported in the bilateral temporal lobe including the left insula, the bilateral superior, middle, and inferior temporal gyrus (Pletzer et al., 2010) as well as the fusiform and parahippocampal gyrus (Pletzer et al., 2015, 2010).

It should be noted that most regions that were found to be increased in OCs compared to naturally cycling women were reported in one study by Pletzer et al. (2010). Pletzer et al. (2010) studied women using hormonal contraceptives (the type of contraceptive was not recorded) in comparison to naturally cycling women in the early follicular and mid-luteal phase. Pletzer et al. (2015) investigated women using OCs in comparison to naturally cycling women in the early follicular phase only. De Bondt et al. (2013a) compared active OC-intake to the luteal phase of the menstrual cycle, whereas Sharma et al. (2020) investigated

Table 1

Summarized results of studies investigating individuals using oral contraceptives compared to naturally cycling individuals.

Type of Analysis	Brain Lobe	Brain Region	Hemisphere	Gray Matter/ White Matter	Increases (↑) and decreases (↓) in OCs	OC vs. NC; Placebo	Correlation	Sample Size n (OC/NC; Placebo)	Age (M ± SD)	MRI analyzing Method	Type of Oral Contraceptive	Study design	Author (Year)
Volume	Whole Brain	Global grey matter	right/left	GM	↓	OC (inactive) < NC	No correlation reported	28/28	21.25 ± 4.02	VBM8 toolbox	combined OC	longitudinal	Lisofsky et al. (2016)
			right/left	GM	↓	OC < NC	GM correlated significantly with estradiol	60/89	22.71 ± 3.20	ROI-based analysis	39 androgenic progestins, 16 anti-androgenic progestins, 5 unknown monophasic combined OCs	cross-sectional	Pletzer (2019)
	Frontal lobe	Total Intracranial Volume	right/left	GM/WM	↓	OC < NC	No correlation reported	44/46	18–40 years	FreeSurfer	cross-sectional	Petersen et al. (2015)	
		Prefrontal cortex	right/left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
			right/left	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
		Inferior frontal gyrus	left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
		Middle and superior frontal gyrus	right/left	GM	↓	OC < NC	No correlation reported	18/20	25.69 ± 4.59	VBM5 toolbox; ROIs	androgenic progestins	cross-sectional	Pletzer et al. (2015)
		Gyrus rectus	right	GM	↑	OC (active) > NC	No correlation reported	27/48	19.68 ± 1.98	VBM8 toolbox	combined OCs, 1st, 2nd, 3rd, and 4th generation progestins	cross-sectional	Sharma et al. (2020)
	Amygdala	Anterior cingulate gyrus	right/left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
			right/left	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
		right	GM	↓	OC (inactive) < NC (follicular)	Not significant after correcting for multiple comparisons	27/38	23.55 ± 3.20	VBM	2nd or 3rd generation progestins	cross-sectional	De Bondt et al. (2016)	
Regional	Prefrontal cortex	Precentral gyrus	right/left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
		right/left	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
	Amygdala	Rolandic operculum	left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
		left	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	

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Table 1 (continued)

Type of Analysis	Brain Lobe	Brain Region	Hemisphere	Gray Matter/ White Matter	Increases (↑) and decreases (↓) in OCs	OC vs. NC; Placebo	Correlation	Sample Size n (OC/NC; Placebo)	Age (M ± SD)	MRI analyzing Method	Type of Oral Contraceptive	Study design	Author (Year)
Parietal lobe	Postcentral gyrus	right	GM	↑	OC (active) > NC (luteal)	No correlation reported	15/15	21.7 ± 0.65	VBM	monophasic combined OCs	cross-sectional	De Bondt et al. (2013a)	
		Supplementary motor area	right/left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
		right	GM	↑	OC (active) > NC (luteal)	No correlation reported	15/15	21.7 ± 0.65	VBM	monophasic combined OCs	cross-sectional	De Bondt et al. (2013a)	
	Supramarginal gyrus	right/left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		left	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
Occipital lobe	Middle occipital gyrus	right	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		Inferior occipital gyrus	right	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
	Occipital lobe	right/left	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
Temporal lobe	Insula	left	GM	↑	OC (active) > NC (luteal)	No correlation reported	15/15	21.7 ± 0.65	VBM	monophasic combined OCs	cross-sectional	De Bondt et al. (2013a)	
		Superior temporal gyrus	right	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)
	Inferior temporal gyrus	right/left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
G	Inferior temporal gyrus	right	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		right/left	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	

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Table 1 (continued)

Type of Analysis	Brain Lobe	Brain Region	Hemisphere	Gray Matter/ White Matter	Increases (↑) and decreases (↓) in OCs	OC vs. NC; Placebo	Correlation	Sample Size n (OC/NC; Placebo)	Age (M ± SD)	MRI analyzing Method	Type of Oral Contraceptive	Study design	Author (Year)
Pletzer et al. (2010)	Temporal pole	right	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		right	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
	Middle temporal gyrus	right/left	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		right/left	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
	Lingual gyrus	right	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		right	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		right	GM	↓	OC (inactive) < NC (follicular)	Not significant after correcting for multiple comparisons	10/38	23.3 ± 3.1	VBM	4th generation progestins	cross-sectional	De Bondt et al. (2016)	
Pletzer et al. (2010)	Fusiform gyrus	right	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		right/left	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		left	GM	↓	OC (active) < NC (luteal)	No correlation reported	15/15	21.7 ± 0.65	VBM	monophasic combined OCs	cross-sectional	De Bondt et al. (2013a)	
	Fusiform face area	right/left	GM	↑	OC > NC (early follicular)	No correlation reported	22/20	24.27 ± 4.55	VBM5 toolbox; ROIs	anti-androgenic progestins	cross-sectional	Pletzer et al. (2015)	
		right	GM	↑	OC > NC (early follicular)	No correlation reported	22/20	24.27 ± 4.55	VBM5 toolbox; ROIs	anti-androgenic progestins	cross-sectional	Pletzer et al. (2015)	
		right/left	GM	↓	OC (inactive) < NC	No correlation reported	28/28	21.25 ± 4.02	VBM8 toolbox	combined OC	longitudinal	Lisofsky et al. (2016)	
Pletzer et al. (2010)	Para-hippocampal gyrus	right	GM	↑	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
		right	GM	↑	OC > NC (mid-luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross-sectional	Pletzer et al. (2010)	
	right/left	GM	↓	OC (inactive) < NC	No correlation reported	22/20	24.27 ± 4.55	VBM5 toolbox; ROIs	anti-androgenic progestins	cross-sectional	Pletzer et al. (2015)		
		right/left	GM	↑	OC > NC (early follicular)	No correlation reported	27/48	19.68 ± 1.98	VBM8 toolbox	combined OCs, 1st, 2nd, 3rd, and	cross-sectional	Sharma et al. (2020)	

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Table 1 (continued)

Type of Analysis	Brain Lobe	Brain Region	Hemisphere	Gray Matter/ White Matter	Increases (↑) and decreases (↓) in OCs	OC vs. NC; Placebo	Correlation	Sample Size n (OC/NC; Placebo)	Age (M ± SD)	MRI analyzing Method	Type of Oral Contraceptive	Study design	Author (Year)
Subcortical structures	Amygdala	left	GM	↓	OC (inactive) < NC	No correlation reported	28/28	21.25 ± 4.02	VBM8 toolbox	4th generation progestins combined OC	longitudinal	Lisofsky et al. (2016)	
	Putamen	right	WM	↑	OC (active) > NC	No correlation reported	27/48	19.68 ± 1.98	VBM8 toolbox	combined OCs, 1st, 2nd, 3rd, and 4th generation progestins	cross- sectional	Sharma et al. (2020)	
	Hippocampus	left	WM	↑	OC(active) > NC	No correlation reported	27/48	19.68 ± 1.98	VBM8 toolbox	combined OCs, 1st, 2nd, 3rd, and 4th generation progestins	cross- sectional	Sharma et al. (2020)	
	Hypothalamus	right/left	GM	↑	OC > NC (mid- luteal)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross- sectional	Pletzer et al. (2010)	
	Pituitary gland	right/left	GM	↓	OC < NC	No significant correlation reported	60/89	22.71 ± 3.20	ROI-based analysis	39 androgenic progestins, 16 anti-androgenic progestins, 5 unknown	cross- sectional	Pletzer (2019)	
Cerebellum	Cerebellum	right/left	GM	↑	OC > NC (mid- luteal)	No significant correlation reported	21/29	22.10 ± 3.70	ITK-SNAP version 3.6	N/A	cross- sectional	Chen et al. (2021)	
	Culmen	right	GM	↓	OC > NC (early follicular)	No correlation reported	14/14	24.55 ± 4.26	VBM5 toolbox	N/A	cross- sectional	Pletzer et al. (2010)	
	Posterior cingulate gyrus	left	GM	↓	OC (inactive) < NC (follicular)	Not significant after correcting for multiple comparisons	10/38	23.3 ± 3.1	VBM	4th generation progestins	cross- sectional	De Bondt et al. (2016)	
Cortical Thickness					OC < NC	Not significant after correcting for multiple comparisons	44/46	18–40 years	FreeSurfer	monophasic combined OCs	cross- sectional	Petersen et al. (2015)	

(continued on next page)

Table 1 (continued)

Type of Analysis	Brain Lobe	Brain Region	Hemisphere	Gray Matter/ White Matter	Increases (↑) and decreases (↓) in OCs	OC vs. NC; Placebo	Correlation	Sample Size n (OC/NC; Placebo)	Age (M ± SD)	MRI analyzing Method	Type of Oral Contraceptive	Study design	Author (Year)
VBM		Anterior cingulate gyrus (caudal)	left	GM	↓	OC < NC	Not significant after correcting for multiple comparisons	44/46	18–40 years	FreeSurfer	monophasic combined OCs	cross-sectional	Petersen et al. (2015)
		Insula	left	GM	↓	OC < NC	Not significant after correcting for multiple comparisons	44/46	18–40 years	FreeSurfer	monophasic combined OCs	cross-sectional	Petersen et al. (2015)
		Orbitofrontal gyrus	right/left	GM	↓	OC < NC	Not significant after correcting for multiple comparisons	44/46	18–40 years	FreeSurfer	monophasic combined OCs	cross-sectional	Petersen et al. (2015)
		Pars triangularis	right/left	GM	↓	OC < Placebo	Not significant after correcting for multiple comparisons	28/25	28.5 ± 3.73	FreeSurfer	0.30 µg ethinyl estradiol/0.15 mg levonorgestrel	longitudinal	Petersen et al. (2021)
Diffusion		Hippocampus (FA)	left	WM	↑	OC (active) > NC	No correlation reported	27/48	19.68 ± 1.98	TBSS	combined OCs, 1st, 2nd, 3rd, and 4th generation progestins	cross-sectional	Sharma et al. (2020)
		Fornix (MD)	right/left	WM	↑	OC > NC	Negative correlation of MD in fornix with estradiol and luteinizing hormone	15/15	21.7 ± 0.65	Manual ROI; Deterministic Tractography	monophasic combined OCs	cross-sectional	De Bondt et al. (2013b)

Note: OC = oral contraceptive group. NC = naturally cycling group. ROI = region of interest. VBM = voxel based morphometry. TBSS = tract based spatial statistics. FA = fractional anisotropy. MD = mean diffusivity. WM = white matter. GM = gray matter. VBM = voxel-based morphometry. TBSS = tract-based spatial statistics.

Increases and Decreases in Brain Volumes in Women using Oral Contraceptives (OCs) compared to Naturally Cycling Women (NCs)

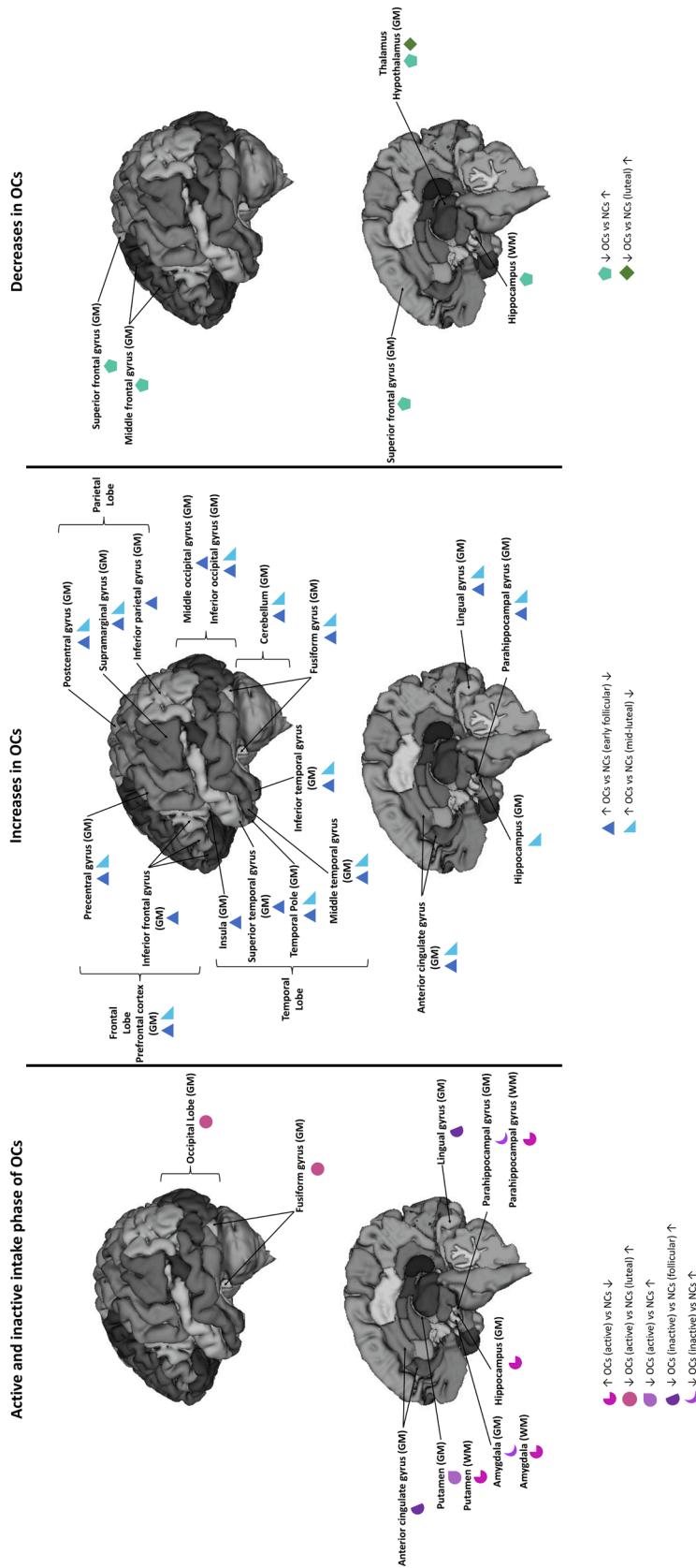


Fig. 1. Summarized results on decreases and increases in brain volumes in women using oral contraceptives (OCs) compared to naturally cycling women (NCs). GM = gray matter. WM = white matter. ↑ = increases in brain volumes. ↓ = decreases in brain volumes.

Table 2

Summarized results of studies investigating single participants over the course of a menstrual cycle.

Author (Year)	Number of MRI images	Menstrual cycle	Hormone levels	Age	MRI method	MRI analyzing method	Results		
							Brain Lobe	Correlations with hormones	Increases (↑) and decreases (↓)
Barth et al. (2016)	2 times 16 (two full menstrual cycles, every 2nd or 3rd day, two scanning sessions 10 months apart)	natural menstrual cycle	typical patterns for estrogen and progesterone levels characteristic for the ovulatory, follicular, and luteal phases of the menstrual cycle, over the course of two cycles in the study	32 years	dMRI	FSL version 5.0.8 using the FMRIB's software library (https://www.FMRIB.ox.ac.uk/fsl)	Temporal Lobe	estrogen (+): FA in bilateral hippocampus gray matter density in left hippocampus estrogen (-): RD in bilateral hippocampus no significant correlations with progesterone reported	no differences reported
Taylor et al. (2020)	30 consecutive days	natural menstrual cycle	estradiol: M = 82.8 pg/ml; range = 22–264 pg/ml progesterone: M = 5.14 ng/ml; range = 5–15.5 ng/ml	23 years	sMRI	CAT12; Automatic segmentation of hippocampal subfields package (ASHS; Yushkevich et al., 2015)	Temporal Lobe	progesterone (+): hippocampal subfields of CA2 and CA3 parahippocampal gyrus progesterone (-): perirhinal gyrus entorhinal gyrus	follicular phase < luteal phase: ↓ hippocampal subfields of CA2 and CA3 ↓ parahippocampal gyrus follicular phase > luteal phase: ↑ perirhinal gyrus ↑ entorhinal gyrus
	30 consecutive days	suppressed menstrual cycle (0.02 mg ethinyl- estradiol, 0.1 mg levonorgestrel)	estradiol: M = 66.2 pg/ml; range = 5–246 pg/ml progesterone: M = 0.15 ng/ml; range = 0.04–0.40 ng/ml	23 years	sMRI	CAT12; Automatic segmentation of hippocampal subfields package (ASHS; Yushkevich et al., 2015)	Temporal Lobe	no significant correlations with estrogen reported no significant correlation reported	no differences reported

Note: dMRI = diffusion MRI. sMRI = structural MRI. (+) = positive correlation. (-) = negative correlation. FA = fractional anisotropy.

the active OC-intake phase in comparison to naturally cycling women in all phases across the menstrual cycle. Following this, the findings of increases and decreases in volumes seem to be dependent on whether the naturally cycling women were split into groups, namely early follicular, follicular, luteal, or mid-luteal phase, and whether women using OCs were split in two groups, namely active vs. inactive intake phase. This suggests that volumetric differences in the brain regions are present between naturally cycling women and those using OCs, however gray matter increases and decreases depend on the phase of the menstrual cycle and the hormonally suppressed cycle by OCs (active vs. inactive). Furthermore, some but not all studies reported whether monophasic combined OCs, androgenic and anti-androgenic progestins, 2nd, 3rd, or 4th generation progestins preparations were used. Hence, the direction of gray and white matter volumetric changes could be the consequence of, first, study participants at different phases of the cycle, and second, different OCs preparations. As of now, no clear pattern of decreases and increases can be identified. For further details, see Table 1 and Fig. 1.

The interplay between brain volumes, hormone levels and OCs has been demonstrated in a longitudinal study on one woman investigating the fluctuating hormonal levels and brain volumes over the course of a natural menstrual cycle and then one year later while on combined OCs (0.02 mg ethinyl-estradiol, 0.1 mg levonorgestrel; Taylor et al., 2020). In this dense series of 30 consecutive MRI scans, endogenous progesterone concentrations were related to gray matter volume in the medial temporal lobe, including the hippocampal subfields, the parahippocampal, entorhinal, and perirhinal gyrus during the natural cycling phase, whereas no such association or volumetric changes were observed during chronic progesterone suppression at the time of use of OCs (see Table 2). This suggests that progesterone shapes the middle temporal gyrus over the course of the natural cycle (Taylor et al., 2020). Moreover, Taylor and colleagues reported that endogenous progesterone serum concentrations during OCs use were comparable to values observed in the early follicular phase of the natural cycle. However, in the aforementioned cross-sectional studies, most volume differences were observed in women using OCs when compared to naturally cycling women in the early follicular phase. This demonstrates that in studies comparing groups of naturally cycling women and OCs users it is very important to compare women according to the follicular and luteal phase, as well as the active and inactive intake phase of OCs, which has been done in some studies, such as by Petersen et al. (2015), but not all studies. Moreover, it is important to keep track of different OC preparations (combined OCs, anti-androgenic, androgenic progestins etc.) as this could also drive the results on increased and decreased volume changes throughout the brain.

4.1.2. Findings on changes in cortical thickness between naturally cycling women and women on OCs

Changes in gray matter volume of cortical brain regions can stem either from changes in cortical thickness, in cortical surface areas, or both. Separating these two measures is important as cortical thickness measures gray matter layer of the cerebral cortex and cortical surface area the surface of the total cerebral cortex. Cortical thinning was reported in the bilateral orbitofrontal gyrus, the left anterior and posterior cingulate gyrus, the left insula in women using combined OCs when compared to naturally cycling women across the whole menstrual cycle (Petersen et al., 2015), as well as the bilateral pars triangularis of the inferior prefrontal cortex (longitudinal study; Petersen et al., 2021) in women using combined OCs when compared to women using placebo (see Table 1).

4.1.3. Findings on white matter volumetric changes between naturally cycling women and women on OCs

One study investigated white matter volumetric changes in women using OCs during the active intake phase compared to naturally cycling women across the whole menstrual cycle. Increases in white matter

volumes were reported in the left parahippocampal gyrus, right amygdala, right putamen, and the left hippocampal volume in the active intake OCs when compared to naturally cycling women (Sharma et al., 2020; Table 1).

4.2. Structural neuroimaging methods

In the next chapters we will review methods that were applied in studies investigating the effect of OCs on the human brain and discuss approaches that are potentially of interest for future studies. Our idea was to make the use of neuroimaging methods in the field of OC-related studies more consistent with the hope to standardize current and future analyses and results.

4.2.1. Manual and semi-automated delineation of brain regions

Manual delineation of brain regions were long considered the ‘gold standard’ given its precision for the target (Chow et al., 2007). The *Insight Segmentation and Registration Toolkit* (ITK-SNAP; <https://www.itksnap.org/>) is a semi-automatic segmentation using both manual and automated delineation to segment structures in MRI images. Chen et al. (2021) used this method to segment the hypothalamus and the pituitary gland and reported decreased volumes in women using OCs compared to naturally cycling women. The authors chose this segmentation method as the hypothalamus and the pituitary gland are known to be very small structures of the human brain. However, manual and semi-automatic delineation methods require manual drawing of region of interest and, are resource intensive. To solve these problems, automated approaches were established to analyze large data sets more efficiently.

4.2.2. Automated delineation of brain regions

Several automated software techniques were developed to analyze human brain morphometry. The most popular methods are *FreeSurfer* and *Voxel-based morphometry* (VBM).

4.2.2.1. FreeSurfer. The FreeSurfer software parcellates regions of the individual brain in an automated fashion. The outputs are the volume, cortical thickness, surface area and gyration index for the cortical brain regions; volumes for subcortical regions, white matter parcellations, and cerebellum for each subject’s brain. The FreeSurfer Software Suite (<https://surfer.nmr.mgh.harvard.edu>) is an open-source software package for processing, analyzing, and visualizing the brain using sMRI images, usually acquired as T1- and T2-weighted images. It was developed by the Laboratory for Computational Neuroimaging at the Martinos Center for Biomedical Imaging in Boston, MA, USA. This software is also the software of choice for the NIH Human Connectome Project (HCP) to map the neural pathways that underlie human behavior (<https://www.humanconnectomeproject.org>). FreeSurfer parcellates the brain into 68 cortical, 70 white matter, and about 18 relevant subcortical regions for each individual (see Fig. 2; <https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/AnatomicalROI/FreeSurferColorLUT>; Fischl et al., 2004). It provides quantitative outputs for individual volumes as well as volumes for total gray and white matter, total cortical volume, and total subcortical volumes. Moreover, it provides surface-based outputs of values for average cerebral cortical thickness, which usually varies between 1 and 4.5 mm (Fischl and Dale, 2000). Given the fact that the cortex is a highly folded sheet of neurons with its surface area mostly buried in folds, FreeSurfer also provides metrics for the total cortical surface area (in mm²; Fischl et al., 1999) and a gyration index (GI). The GI is defined as the ratio of the inner cortex buried within the folds to the outer cortical surface (Zilles et al., 1989, 1988). A cortex with extensive folding has a larger GI whereas a cortex with less folding has a smaller GI (Schaer et al., 2008). Gyration allows a larger cortical surface area and, therefore, more functional volume/neurons to fit inside the cranium (Rakic, 2009).

FreeSurfer was applied by Petersen et al. (2015, 2021) to explore

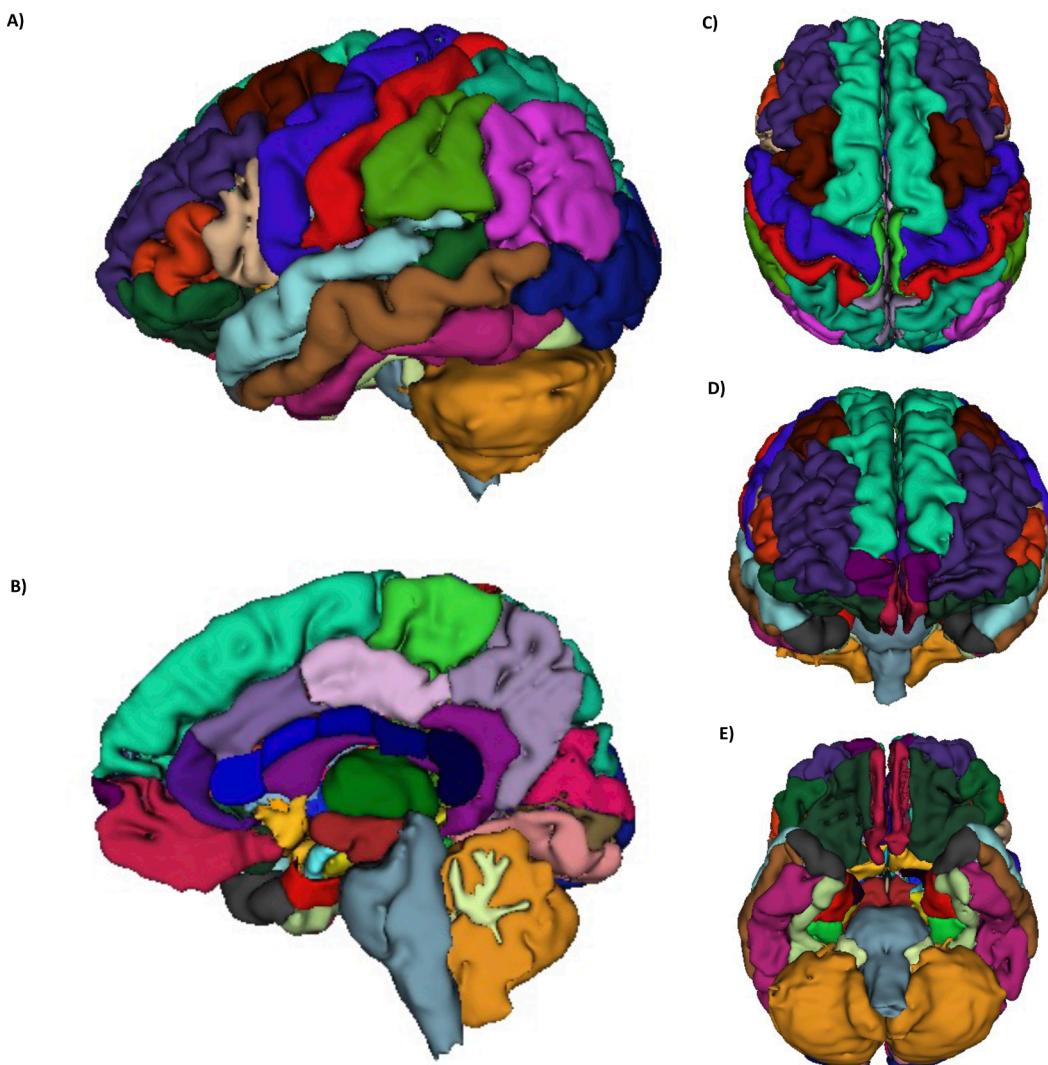


Fig. 2. 3D FreeSurfer Parcellation of the human brain. Each parcellation is represented in a distinct color. Brain parcellations were visualized in 3DSlicer software. Panel A shows lateral view and Panel B shows medial view. Panel C shows a superior view. Panel D shows a frontal view. Panel E shows an inferior view. Red lines represented the borders of the frontal, parietal, occipital, and temporal lobe of the brain.

changes in brain regions in women using combined OCs. Cortical thickness was reduced in lateral orbital cortex and the posterior cingulate cortex in women using OCs compared to naturally cycling women. Changes in cortical thickness can reflect reorganization or loss of neurons/connections within the cortical layers.

In addition to the above mentioned parcellations, FreeSurfer is being developed to improve automated segmentations for several other regions of interest to the OCs research community. The hypothalamus and hypothalamic subunits can now be segmented using FreeSurfer version 7.2 (<https://surfer.nmr.mgh.harvard.edu/fswiki/HypothalamicSubunits>; Billot et al., 2020), the hippocampal subfields and amygdala can also be now segmented using FreeSurfer version 6 or higher (<https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfieldsAndNucleiOfAmygdala>). However, the pituitary gland cannot be assessed by FreeSurfer as of yet. The gland is being removed during the process of making the mask of the brain to strip the skull and needs to be delineated either manually or via semi-automated segmentation, as performed by Chen et al. (2021) mentioned above.

Gyration has not been explored in the studies in use of OCs yet. It is often being viewed as an index of early developmental pathology (Schaer and Eliez, 2009). However, it can also be influenced by maturation, for instance, in adult female patients with MDD, reduced cortical

gyrification was found in the precuneus, the superior parietal gyrus, the parahippocampal gyrus, the middle frontal gyrus, and the fusiform gyrus compared to age-matched control females. Moreover, hypogyrification was significantly associated with number of depressive episodes (Deppeping et al., 2018). Given the incidence of depressive episodes in women using OCs, the GI might be explored in context of clinical symptoms. All in all, FreeSurfer is a powerful tool that offers many measures from the analysis of the whole brain using sMRI.

4.2.2.2. Voxel-based morphometry. VBM allows comparison of brain gray matter between two groups of individuals, such as healthy controls and patients or women using OCs and those not using OCs. VBM involves a voxel-wise comparison of gray matter between groups and therefore analyzes all of the voxels in the brain (Ashburner and Friston, 2000). It follows 12 distinct steps (Kurth et al., 2015) using an affine and a non-linear registration which generally registers MRI image of each individual to a template. The most popular VBM tools are the VBM8 toolbox and the Computational anatomy toolbox 12 (CAT12; <https://www.neuro.uni-jena.de/cat/>), designed by the Structural Brain Mapping Group at the Jena University Hospital (Jena, Germany). The results from the VBM method are voxels or cluster of voxels of statistically significant differences between groups tested. The location of the clusters is given in the

Montreal Neurological Institute and Hospital (MNI) coordinates, a normalized space defined in SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>), and then matched to brain regions using a gray matter atlas (e.g. Desikan-Killiany Atlas, Desikan et al., 2006; Destrieux Atlas, Destrieux et al., 2010). As in FreeSurfer, VBM also offers the investigation of cortical thickness, cortical surface area, and gyration.

In studies assessing the effects of OCs use in women, Lisofsky et al. (2016), Pletzer et al. (2010), Sharma et al. (2020), and De Bondt et al. (2013a) used VBM to compare brain volumes between OCs and naturally cycling women. Clusters of voxels with statistically significant differences of increased and decreased brain volumes between groups were reported in frontal, parietal, occipital, temporal lobes, subcortical structures, and cerebellum.

5. Diffusion neuroimaging

Diffusion MRI (dMRI) provides insight into the tissue microstructure, such as cell organization, myelination, and directionality of fiber bundles in the brain (Basser et al., 1994; Beaulieu, 2002; Kikinis et al., 2016; Song et al., 2002). DMRI, also called Diffusion Tensor Imaging (DTI), has become the tool of choice to explore brain microstructure *in vivo*. The dMRI method is mostly known for the analysis of brain white matter but most recently developed tools also explore the gray matter. DMRI is a non-invasive way of probing the diffusion of water in biological tissues (Basser et al., 1994). Changes in white matter microstructure can be quantified by using the most common diffusion indices, such as fractional anisotropy (FA), axial (AD), radial (RD), and mean diffusivity (MD), which characterize changes in the diffusion profile of water molecules and are thought to be indicators of integrity of white matter (Beaulieu, 2002; Song et al., 2002).

In the following chapters, we will summarize studies using dMRI methods to explore changes in brain white matter in women using OCs and across the female menstrual cycle. Thereafter, we will review the methods that were applied in studies investigating the effect of OCs on the human brain and discuss approaches that are potentially of interest for future studies.

5.1. Findings from diffusion MRI

So far, only two cross-sectional studies compared white matter microstructure in women using OCs and naturally cycling women (see Table 1; De Bondt et al., 2013b; Sharma et al., 2020). One study focused on the hippocampus and observed increased FA in the left hippocampus in women using combined OCs compared to naturally cycling women (Sharma et al., 2020). The second study reported increased MD in the fornix, a fiber bundle which acts as the major output tract of the hippocampus, when women using combined OCs (scanned twice) were compared to naturally cycling women (first scan in the follicular phase, and a second scan in the luteal phase of the menstrual cycle). The increase in MD of the fornix was more significant when women using OCs were compared to naturally cycling women in the luteal phase (De Bondt et al., 2013b). In addition, MD correlated negatively with plasma concentrations of LH and endogenous estradiol in the whole sample, suggesting that increased MD was associated with lower hormonal levels.

Of interest is a third dMRI study that did not compare groups of women on OCs to naturally cycling women but performed a dMRI study of the hippocampus in one woman across the menstrual cycle. Barth et al. (2016) performed a longitudinal study on a single naturally cycling woman investigating the fluctuating hormonal levels and changes in the hippocampus. Thirty dMRI scans were acquired over the course of a full menstrual cycle revealing a positive association between fluctuations of the endogenous estrogen concentrations and changes in bilateral hippocampal FA (see Table 2; Barth et al., 2016). Hence, hippocampal FA peaked during the follicular phase when the estrogen levels are the highest. A second important finding in this study is that, apart from FA,

RD correlated with estrogen levels, however in the opposite direction. Increases in FA and decreases in RD, in relation to the estrogen levels, might be a signature of increased degree in myelination of the axons upon increasing hormonal levels across the menstrual cycle. This suggests substantial dynamics of plasticity in the hippocampus during the menstrual cycle.

5.2. Diffusion neuroimaging methods

5.2.1. Tract-based spatial statistics

There are several methods to analyze images from dMRI and to compare dMRI output measures between groups of participants. Similarly to the methods used to analyze sMRI images, the method of *Tract-based spatial statistics* (TBSS) is based on the VBM approach and has been designed to compare groups of participants. It is the most popular method examining the white matter of the whole brain. TBSS is an open access software (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>), and analyzes a skeletonized version of the major white matter tracts in the brain (Smith et al., 2006). The results from the TBSS analysis are voxels of the white matter skeleton, demonstrating statistically significant differences between the groups compared. TBSS can analyze FA, MD, RD and AD maps from dMRI.

The TBSS method was used by Sharma et al. (2020) to explore the effect of OC on brain white matter between OC user and naturally cycling women. FA in the left hippocampal white matter was increased in women using OC.

Based on the TBSS approach, the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) consortium (<https://enigma.ini.usc.edu/>), developed a standardized dMRI protocol to extract dMRI phenotypes to provide global and regional measurements across diverse neuroimaging protocols to allow pooling of findings from multiple studies (Jahanshad et al., 2013). The ENIGMA consortium has initiated an international effort bringing together researchers to understand brain structure, function, and disease, based on brain imaging data. The consortium has formed working groups focused on various diseases and phenotypes, with most groups combining data of 10,000 samples and more (Thompson et al., 2020, 2014). The working group interested in the exploration of the effect of OCs and women health remains to be set up.

5.2.2. Fiber tract reconstruction and analysis

Another application of dMRI is *fiber tract reconstruction*, a method called the *tractography* or *diffusion tensor tractography*. Tractography is a technique to reconstruct neural ‘tracts’ in the brain white matter, which allows to identify, to visualize, and to quantify cortico-cortical, cortico-subcortical and cerebellar connections within and between individuals. However, it should be noted that tracts represent at best the major fiber tracts of white matter and not individual fibers or nerves. The limitation of the resolution of the fiber tracts is set by the voxel size of the dMRI image which are typically on mm³ scale (for instance HCP data set). Tractography allows to reconstruct fiber tracts in each individual without image registration and alignment to a common space (such as MNI or Talairach coordinates in TBSS). Accordingly, tractography can be applied even if the location of the tract varies across individuals, which is often the case (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Conturo et al., 1999; Mori & Barker, 1999).

There are several techniques to reconstruct fiber tracts. The two major approaches are the *probabilistic* and the *deterministic tractography*. The probabilistic and the deterministic tractography techniques use algorithms, which follow the principal diffusion direction to reconstruct the tract. The deterministic tractography is in general less computationally intensive than the probabilistic tractography, but both allow the reconstruction of the tracts of the entire brain. The first approach to deterministic tractography, the *single tensor tractography*, computes one tensor of the FA in each voxel to reconstruct the tract from voxel to the next voxel. A tensor, explained in very simple terms, provides a

mathematical description of the rate of diffusion in three orthogonal directions (Le Bihan et al., 2001). Single tensor tractography works well for the majority of fiber tracts, especially those that have densely packed axons.

De Bondt et al. (2013b) used single tensor deterministic tractography to reconstruct four major white matter fiber bundles, namely corpus callosum, cingulum, fornix, and corticospinal tract in naturally cycling women and in those using OCs and reported that MD in the bilateral fornix was increased in women using OCs compared to naturally cycling women.

While single tensor deterministic tractography works well for most of the major fiber tracts, crossing and fanning fibers within a voxel make this method problematic because the algorithm calculates only a single tensor that may follow an incorrect tract or even stop (Basser et al., 2000). The *multi-tensor tractography* and the probabilistic tractography,

however, perform better in regions of crossing and fanning fibers, are more accurate, and can identify multiple tracts within a voxel (Lifshits et al., 2009). The multi-tensor tractography can detect the smaller tracts because it allows, based on the FA calculated for two or more tensors in every voxel, a more meaningful continuation of the tract reconstruction (Malcolm et al., 2010; Peled et al., 2006).

Once all possible tracts are created for the entire brain, the major anatomical fiber tracts/connections can be extracted from whole brain tractography using automated or semi-automated parcellation techniques. Those include *White matter query language* (WMQL; Wassermann et al., 2012), *TRAct Constrained by Underlying Anatomy* (TRACULA; <https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula>), *TractSeg* (Wassermann et al., 2018), *fiber clustering*, or *Deep learning tractography segmentation* method (DeepWMA; Zhang et al., 2018; see Fig. 3 as an example of the later). Finally, results from the tractography parcellation

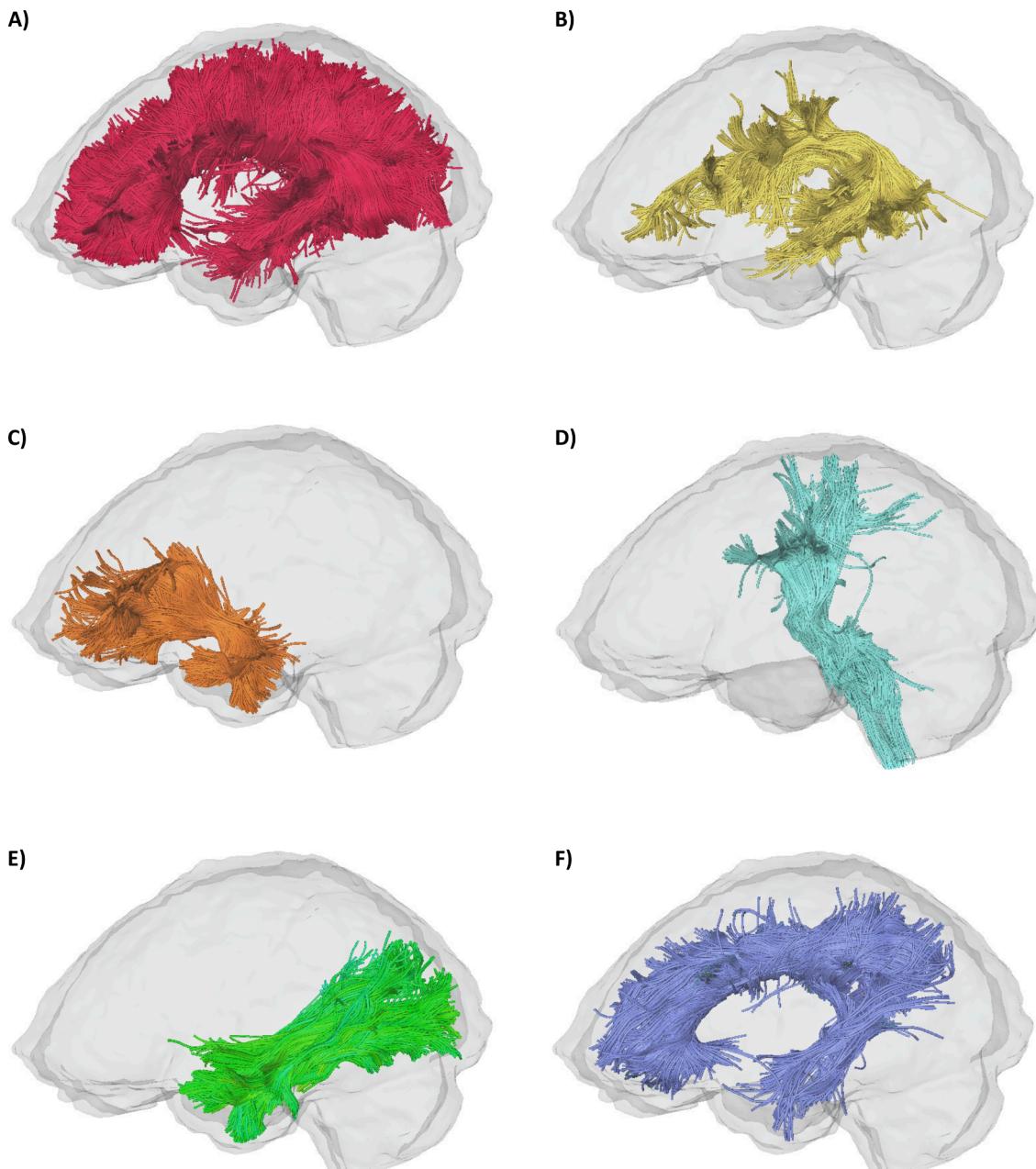


Fig. 3. 3D reconstruction of six major white matter tracts of the human brain. Corpus callosum (CC) in panel A, Arcuate fasciculus (AF) in panel B, Uncinate fasciculus (UF) in panel C, Corticospinal tract (CST) in panel D, Inferior longitudinal fasciculus (ILF) in panel E, Cingulum bundle (CB) in panel F visualized using 3D Slicer software. Fiber tracts were reconstructed using multi-tensor tractography and clustering.

can be displayed using one of many available visualization platforms (such as 3DSlicer; <https://www.slicer.org/>), and the diffusion metrics (FA, MD, AD, RD) can be calculated for each tract and each individual, and used in statistical analysis.

5.2.3. Measures of dMRI and of white matter microstructure

As mentioned above, changes in white matter microstructure can be identified by making use of the most common diffusion indices FA, AD, RD, and MD, which characterize changes in the diffusion profile and are thought to be indicators of integrity of white matter. FA is an index that describes the degree of the anisotropy of diffusion and, therefore, likely reflects axonal density, coherence and myelination in white matter. FA has a value between zero and one. A value of zero means that the diffusion is isotropic (the water molecules are unrestricted in all directions). A FA value of one represents diffusion that is restricted along a single direction, hence it is anisotropic (Kingsley, 2006). Accordingly, in areas of high orientation coherence, such as in white matter, FA is high. FA is lower in gray matter and close to zero in cerebrospinal fluid (CSF). Thus, a decrease of FA index in white matter is thought to reflect a reduction of tract integrity (Beaulieu, 2002; Song et al., 2002). Although FA is sensitive to even small changes, it is thought to be a rather non-specific measure. To better understand the microstructure of the tissue it is recommended to use additional diffusion measures, such as AD and RD, which demonstrate more specific relationships with white matter pathology. Changes in AD, in addition to changes in FA, appear to be more specific to axonal degeneration, whereas changes in RD could be modulated by myelin in white matter (Alexander, Lee, Lazar, & Field, 2007). MD is the average rate of diffusion and is an inverse measure of membrane density (Chen et al., 2013). Increased MD reflects a disruption of white matter microstructure and in special cases demyelination (Oh et al., 2009).

In OC-related studies, left hippocampal FA was found to be increased in women using OCs during the active intake phase when compared to naturally cycling women (Sharma et al., 2020). Over the course of a full natural menstrual cycle, FA in the bilateral hippocampus correlated positively whereas RD correlated inversely with endogenous estrogen plasma levels (Barth et al., 2016). The authors speculated that the changes in FA and RD maybe a signature of changing myelination of axon in association to fluctuating estrogen concentration during the menstrual cycle. This interpretation of changes in myelination of the hippocampal axons is intriguing; however, we need to be aware that changes in FA and RD describe changes in water diffusion in tissues and do not provide any further biological meaning. The changes in myelination being associated with changes in FA and RD is based on findings that were validated in animals and in postmortem studies on schizophrenia patients. Changes in axonal myelination might also apply to the menstrual cycle and to the effect of OC use which remains to be validated. In female and male individuals with chronic schizophrenia, for instance, decreased FA and increased RD were repeatedly reported in several white matter tracts throughout the brain (Kelly et al., 2018). The link between the dMRI measures and demyelination of the axons in schizophrenia is based on, first, a series of experiments in animals that has demonstrated that demyelination of axons is reproduced by increased RD and decreased FA, with AD unchanged (Song et al., 2005, 2003) and, second, in post-mortem studies on the brains of schizophrenia patients where abnormalities in myelination of fibers, altered oligodendrocytes, and changes in the expression profiles of myelin-related genes were reported (Hakak et al., 2001; Haroutunian et al., 2007; Haroutunian and Davis, 2007; Tkachev et al., 2003; Uranova et al., 2001). It is very likely that the observed changes in FA and RD and the estrogen concentrations during the menstrual cycle reflect remodulation of myelin in the hippocampal white matter, however, it should be validated in animals using dMRI imaging and in histological preparations of myelin staining (Pistorio et al., 2006).

In addition to the most common dMRI measures such as FA, MD, AD, and RD, which are derived from tensor model, another measure, the

FreeWater (FW), might be relevant to the study of use of OCs and of the menstrual cycle. Extracellular water is referred to as CSF in the ventricles, edema, or fluid around the brain parenchyma. However, it can also be found in the extracellular spaces of gray and white matter. Since water diffusion can be influenced by extracellular water, (Beaulieu, 2009; Schwartz et al., 2005; Takahashi et al., 2000), separating cellular and extracellular water signal can increase specificity of diffusion measurements. The assessment of these water fractions in the brain can be obtained using the FreeWater model (Pasternak et al., 2009). Measuring extracellular water (FreeWater, FW) might provide important information about extracellular processes such as atrophy and neuroinflammation in various clinical as well as healthy conditions (Metzler-Baddeley et al., 2012). Cellular water diffusion fraction (known also as corrected FA, or FA tissue (FAt) has been shown to be sensitive to cellular changes in Alzheimer's disease (Bergamino et al., 2021), Parkinson's disease (Ofori et al., 2015), aging (Chad et al., 2018), depression (Bergamino et al., 2016), eating disorders (Kaufmann et al., 2017), as well as schizophrenia (Lyall et al., 2018). In addition, the effects of extracellular water on diffusion metrics can be removed and was shown to improve tract reconstruction (Pasternak et al., 2009). So far, no such analysis was performed in individuals using OCs. FW might potentially be relevant to assess effects of OCs intake because several studies reported increased inflammatory blood markers (Divani et al., 2015; Hinton et al., 2006; Piltonen et al., 2012) and body fluid retention among young adult women using hormonal contraceptives (Stachenfeld et al., 1999), as well as fluctuating water content across the menstrual cycle (Graham et al., 1995; Tomazo-Ravnik and Jakopić, 2006), and reduced volume of CSF at time of ovulation (Hagemann et al., 2011). However, studies investigating the effect of OCs and the female menstrual cycle did not focus on either extracellular water or CSF.

5.2.4. Neurite orientation dispersion and density imaging

Another model, that improves biological specificity of diffusion measurements and gained huge popularity in research community, is the *neurite orientation dispersion and density imaging* (NODDI) method (Zhang et al., 2012). The NODDI technique estimates the microstructural complexity of dendrites and axons and is thought to provide more specific markers of microstructural tissue changes compared to FA, RD, AD, and MD. The metrics derived from NODDI are the neurite density index (NDI; also called intracellular volume fraction), the orientation dispersion index (ODI), and the isotropic volume fraction (IsoVF). NODDI has been applied to uncover microstructural changes in gray and white matter of multiple mental disorders (Kamiya et al., 2020). As example, NODDI was applied to the analysis of fornix and to the hippocampal subfields in an aging study and revealed that changes in the neurite density index correlated with memory performance, which demonstrates that these measures captured neurobiological properties that related to performance on a task (Radhakrishnan et al., 2020). Given that neurites can remodel fast, this method offers an opportunity to monitor neuroplastic changes in a noninvasive way. The NODDI method is of interest to further explore the reported changes in hippocampus, as well as in brain white and gray matter, in relation to fluctuating concentration of estradiol and progesterone during the menstrual cycle and in non-cycling women. No such analysis has been published/reported so far. NODDI requires more complex scan acquisitions (multi shell acquisition protocols) which are included in the acquisition protocol of HCP, but not used earlier, making the NODDI method less accessible for data sets already acquired.

5.2.5. Gray matter microstructure

dMRI is the tool of choice to explore microstructure of brain white matter, as discussed above, but it has been applied to investigate microstructure of cortical gray matter. A novel measure, the so called *gray matter heterogeneity*, is used to characterize the variability in tissue microstructure within a specific region from dMRI. This is important as changes of microstructure in gray matter might go unnoticed due to the

absence of macrostructural volume changes. Using dMRI in white matter, most studies look at average values of the given dMRI measures of FA, RD, AD, and MD and compare these between groups. Gray matter heterogeneity, though, looks at the ‘variability’ of these measures within a specific gray matter region (Rathi et al., 2014). Following this, the variability in gray matter microstructure can be described by the heterogeneity of diffusion measures in FA (HFA), AD (HAD), RD (HRD), or MD (HMD) and can be used on legacy data sets that were acquired using single shell acquisitions (Rathi et al., 2014).

The gray matter heterogeneity was compared between individuals with schizophrenia and healthy controls. Heterogeneity in FA in the frontal lobe was increased in people with schizophrenia, which might be the result of abnormal maturation in gray matter during neurodevelopment and a disorganized pattern of gray matter microstructure (Seitz et al., 2018). Similarly, in young adults with 22q11 Deletion Syndrome, heterogeneity in FA in the limbic area correlated with executive performance, demonstrating that this measure of microstructure captures a, so far unknown, biological feature that relates to the individual’s performance (Kikinis et al., 2019). No such analysis has been performed in women using OCs yet. It would be of interest to explore whether use of OCs in adolescents and young adults might have an effect on maturation of gray matter and could be investigated using the gray matter heterogeneity method.

6. Summary of results and methods

In summary, relatively few imaging studies have been performed to answer the question of the effect of OCs on the brain. The majority of existing studies compared brains of women who were or were not using OCs and most studies had relatively small numbers of participants (approximately 20 individuals) per group. Changes in cortical, subcortical, and cerebellar gray matter were reported and changes in the connecting white matter fibers are likely. As demonstrated for hippocampal white matter and the fornix, there are changes in microstructure of brain white matter between naturally cycling women and those using combined OCs. There was a significant attentiveness to explore the hippocampal structure. However, other brain regions like the hypothalamus and pituitary gland are of special interest as these parts of the brain regulate, express, and produce sex hormones. Therefore they are potential targets for the effects of OCs by chronically diminishing the endogenous concentration of these hormones.

We have further learned from the published studies that it is important to compare women during the follicular vs. luteal and active vs. inactive OC-intake phase, as well as to form groups with the same OCs types.

We have provided a closer look at the most popular methods to extract and to quantify macrostructural and microstructural changes between groups of women using OCs and naturally cycling women. We further discussed biological specificity of those methods, and presented newer methodologies that hold promise for OCs research.

This review emphasizes that the potential of these techniques has not been exhausted as of yet, and it will be beneficial to perform additional sMRI and dMRI studies to understand the underlying white and gray matter changes associated with the use of OCs, as well as their biological specificity.

7. Translational approach between animal and human research

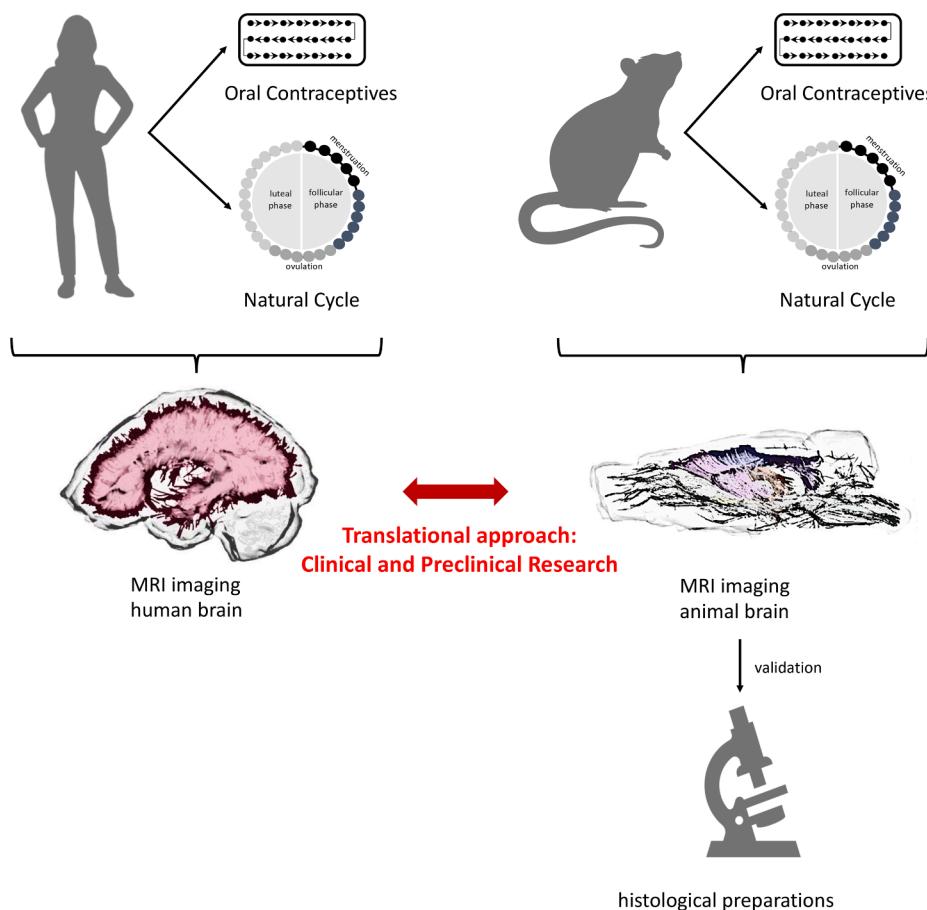
Imaging methods, sMRI and dMRI, as used in clinical research are very powerful tools that can detect even very subtle changes in brain structures in a non-invasive way. Although sMRI and dMRI provide information about the biological/morphological features of the changes observed in the here reported studies, these imaging methods do not provide information about the underlying biological mechanisms. Imaging studies focusing on the menstrual cycle and the effect of OCs on the brain, however, are scarce. In order to learn about the underlining

biological mechanisms, experiments in animals can be helpful. Animal research has a large range of experimental methods that can provide information at the cellular and molecular level by using histological preparations of the animal tissues. In addition, animal research makes it possible to explore the mechanisms of effects of OCs on the brain in relation to neuroimaging biomarkers. Animal models have previously served to increase our knowledge regarding the mechanisms involving endogenous and synthetic hormones by using methods like histological analyses including pathway enrichment analysis, (Westernblot analyses; e.g. Diaz and Raval, 2021), immunoassays of brain tissues (e.g. Pluchino et al., 2009; Simone et al., 2015), in-situ-hybridization for densitometry (e.g. Simone et al., 2015), spine density analysis (Leranth et al., 2002), and optogenetics (e.g. Johnson et al., 2020). The investigation in animal and human research can become complementary by using imaging methods in animals that are used in clinical animal settings investigating the effects of OCs (see Fig. 4).

With regards to cross-species translational approaches involving OCs, Graham and Milad (2013), for instance, investigated OC-related effects on fear extinction in female rats as well as in women. They demonstrated that in female rats and humans fear extinction is impaired during OC treatment. Since it is not easy or ethical to change or manipulate contraceptive treatment in women, Graham and Milad used the rat as an animal model to investigate the potential underlying mechanisms more closely. First, they observed that hormonal contraceptive termination in rats prior to extinction learning reversed the adverse effects of hormonal contraceptives on fear extinction. The hormonal state during fear conditioning did not play a role. Second, the authors investigated whether fear extinction could be restored without OC termination by increasing the levels of available estradiol via injection of systemic estrogen agonists or vehicles. With regards to fear extinction, the injection of estrogen agonists indeed prevented any impairments, whereas the vehicle condition did not show this effect. Translating the observed findings, Graham and Milad administered a dose of estradiol or placebo to OC using women prior to extinction learning and were able to successfully replicate their findings from the animal experiments. Overall, Graham and Milad (2013) provide an example on how knowledge of the effect of OCs on the brain can be gained. Furthermore, they demonstrate that these OC-related effects can be tested in animal studies and successfully translated into human studies. However, it would have been indeed interesting to also investigate the neural mechanism underlying the OC-effect on fear extinction.

Using imaging methods to study the menstrual cycle and the effect of OCs on the brain, however, are scarce. Nevertheless, Qiu and colleagues (2013) used high-resolution ex-vivo as well as in-vivo MRI in a mouse model to gain insights in the role of the estrous cycle on hippocampal volume and its relation to cognition. The ex-vivo MRI experiment demonstrated that hippocampal volume in mice of adjacent estrous cycle phases can differ up to 2.8 %. Furthermore, the hippocampal volumes of the mice, that were sacrificed right after performing a T-maze, predicted what cognitive strategy the mice would use to solve the maze. The in-vivo experiment, which was a within-subject design, confirmed the findings of the cross-sectional ex-vivo MRI analysis (Qiu et al., 2013). Therefore, this study highlights not only the hormone-related brain plasticity in the hippocampus and its influences on cognition, but also the feasibility of investigating hormone-related effects of the brain using MRI in animal models.

There are several further findings of hippocampal plasticity where animal models and translational approaches would be highly interesting. For instance, increases in FA and decreases in RD in hippocampal white matter were reported in humans during the natural menstrual cycle and were associated with fluctuating levels of estrogen. The authors interpreted the changes as reorganization of axonal myelination (Barth et al., 2016). This interpretation could be tested in rodent females during the estrus in a series of imaging the animal using dMRI, then sacrificing the animal and staining brain slices using myelin staining through the estrus cycle. Similarly, a study comparing women using OCs



to naturally cycling women reported increases in FA in the hippocampal white matter using the TBSS method (Sharma et al., 2020), which could also be investigated in the rodent brain and followed *in situ* for changes

in myelination in rodents that were administrated OCs and those that cycle naturally. The potential findings of changes in myelination in animal models would translate the findings from animal to human via

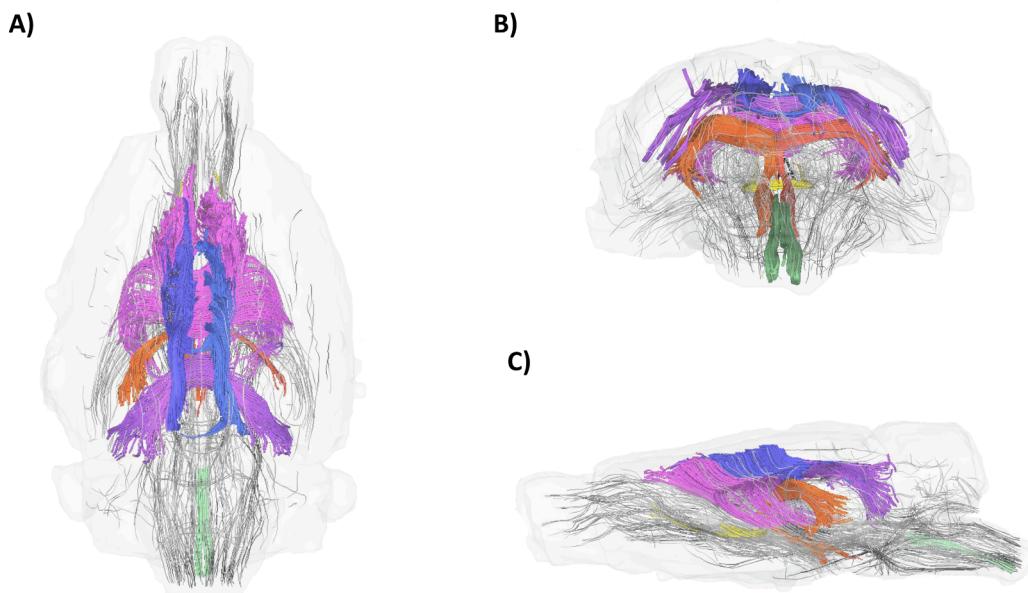


Fig. 5. 3D visualization of white matter fiber bundles of the rat brain using 3D Slicer software. Panel A shows a superior view. Panel B shows a frontal view. Panel C shows a lateral view. Cingulum bundle (CB) is represented in blue. Corpus callosum (CC) in pink and purple. Fornix is represented in orange. Spinothalamic tract (STT) is represented in green. All other fibers of the tractography analysis in gray. Fiber tracts were reconstructed using single tensor tractography of the entire rat brain, then regions of interest were drawn manually to select the specific tracts.

the imaging method.

Animal models can help us to understand the effects of endogenous sex hormones on the brain and mood (e.g. Li et al., 2012). The constraint of applying clinical imaging studies to animals was the lack of rat and mouse brain atlases that allow segmentation of the brain. However, progress has been made by introducing the SIGMA rat brain templates and atlases (Barrière et al., 2019), as well as the processing pipeline for atlas-based imaging data in the mouse brain (AIDAmri; Pallast et al., 2019). An example of a tractography performed on a rat brain is shown in Fig. 5. These new approaches will be helpful to translate knowledge between animal models and human studies in OCs. Communication among scientists about findings derived from both, humans and animals studies, will allow for a rigorous planning of the most suitable types of experiments and the interpretation of the findings. A collaboration among experts in animal, imaging and clinical studies can make translational research successful. Together, an interdisciplinary team of experts can make greater leaps in our understanding of the brain on OCs than one modality or type of research could hope to accomplish.

8. Outlook and implications for future research

While this review has focused on structural imaging, there is vast body of research investigating OCs in women using functional MRI (reviewed in Brönnick et al., 2020; Montoya & Bos, 2017). Future studies may want to consider combining structural and functional imaging to complement each other, thereby enhancing our understanding of the brain's functionality and morphometry. Moreover, it will play a pivotal role in clinical applications as the goal of multimodal neuroimaging is to improve early detection of brain abnormalities (Martí-Bonmatí et al., 2010). Neuroimaging studies might be helpful to identify the effect of OCs on women's brains and the associated changes in factors related with mental health such as depressive and anxious states. Currently, there is a lack of sMRI and dMRI studies assessing the effect of OCs on mental health. Future studies should include the measurement of factors associated with mental health such as mood and self-concept in combination with neuroimaging markers. This integrative approach will allow to explore the relationship between mental health and brain architecture in women with different hormonal profiles (including women using hormonal contraception). As hormonal levels show a great change across the female life and across the menstrual cycle, longitudinal studies comparing naturally cycling women to women using OCs over time and at different life stages are of particular importance. Accordingly, it is important to assess at what age participants started to take OCs, for how long, and what type of OC. Future studies could also aim for assessing adolescent women that just started to use OCs, pregnant women, postpartum women, and women during the menopausal transition to inform about the effects of potential gray and white matter changes in times of hormonal transition periods (Rehbein et al., 2021). Most studies, though, rely on cross-sectional data. To expand our current knowledge of imaging the brain on OCs, it would be valuable to have large data sets which would significantly increase statistical power. The requirement for subgroups, analysis of large number of brain regions, and brain white matter tracts requires large study samples. A feasible approach to obtain larger cohorts is using standardized protocols and standardized analysis methods to allow rigorous comparison of findings across studies and/or pooling data sets from several sites. This can be achieved by pursuing, in parallel, two approaches: one, to aggregate already existing data sets and process them using meta-analysis and harmonization platforms (like the ENIGMA Consortium), and second, acquire new data with standardized acquisition protocol, standardized postprocessing methods, standardized behavioral, clinical measures, standardized OCs intake and phase of the cycle across multiple research sites. For example, the Human Connectome Project (HCP; <https://www.humanconnectome.org>), the UK biobank (<https://www.ukbiobank.ac.uk>), and the Adolescent Brain Cognitive Development (ABCD) Study (<https://nda.nih.gov/abcd>), and others, are acquiring imaging data for

the purpose of comparing images across multiple populations and across life span. The NIH Toolbox has been developed to assess standardized neurological and behavioral function across diverse populations and life span of age 3 to 85 years (https://en.wikipedia.org/wiki/NIH_Toolbox). Collecting standardized images, behavioral and clinical measures, informing about mental health aspects, in naturally cycling women and women using OCs would be a great addition to the already collected images from other populations and ages.

9. Conclusion

Changes in gray and white matter in brains of women taking OCs suggest that OCs have an effect on brain architecture. There is still a lot of work to do in order to understand the positive and the negative effects of OCs on women's brain and wellbeing and imaging methods are helpful tools in this quest. We believe that one of the steps towards understanding the effects of OCs will be achieved in following a translational approach by applying clinical imaging methods not only to humans but also to animals and that these animal experiments will be backed up with histological, cellular, or molecular experiments. Furthermore, human studies with larger sample sizes will achieve consistent findings and understanding the effect of hormonal contraceptives on women's brain and women's health across specific stages of life.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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