

Oral contraceptive pills reduce prefrontal cortical thickness

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Observational studies report conflicting effects of oral contraceptive pills on brain structure

The ovarian hormones estrogen and progesterone are regulators of synaptogenesis (Fester et al., 2012; McEwen & Woolley, 1994; Sasahara et al., 2007; Sato et al., 2007) and neurogenesis (Fowler et al., 2008; Li et al., 2011; Suzuki et al., 2007).

Oral contraceptive pills (OCPs) reduce endogenous levels of progesterone and 17 β -estradiol.

OCPs linked to **smaller** brain regions OCPs linked to **larger** brain regions

Petersen et al., 2015

De Bondt et al., 2013

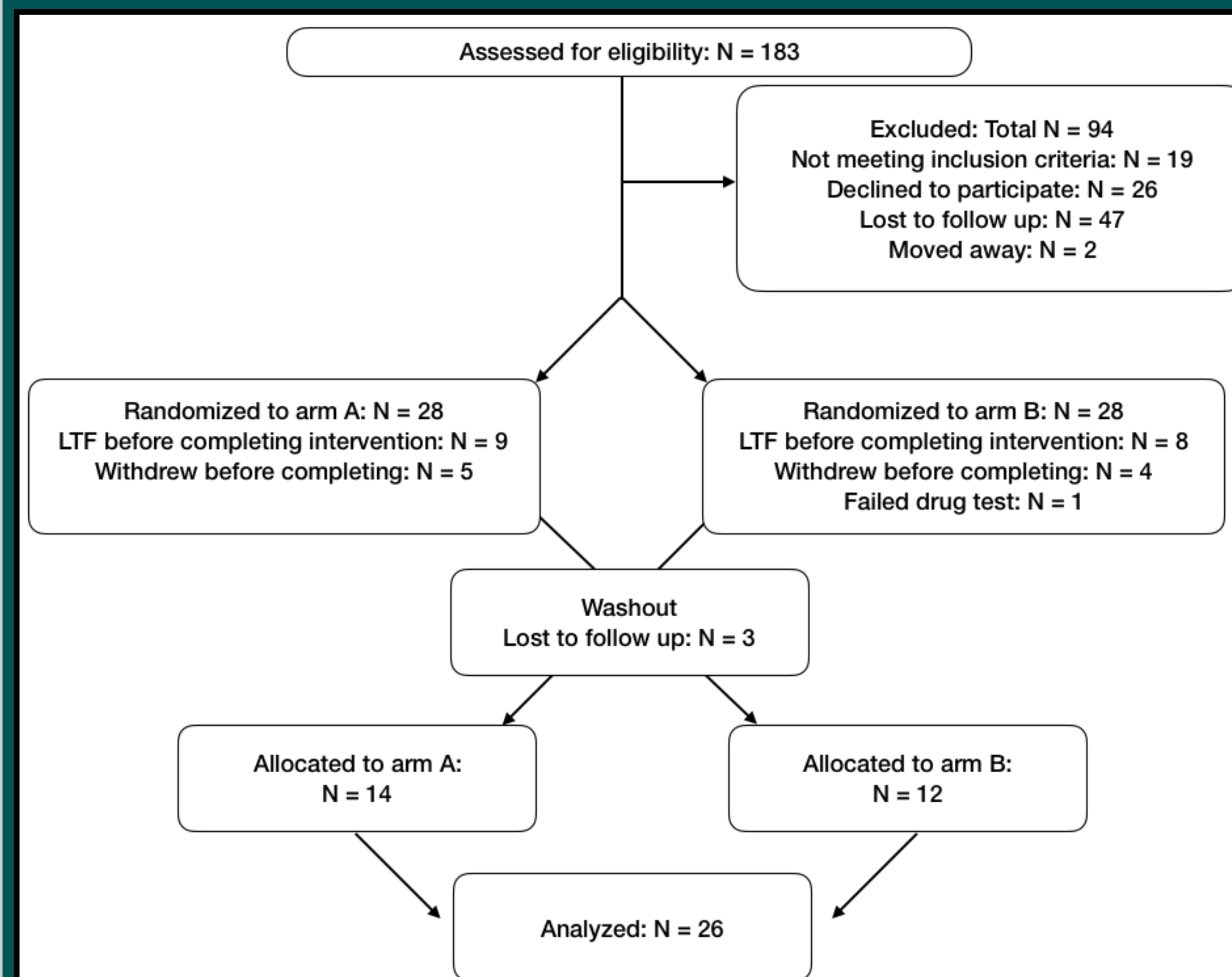
Pletzer et al., 2010

Observational studies have found conflicting effects of oral contraceptive pills on mood disorders

Epidemiological studies reported lower rates of subthreshold panic disorder (Cheslak-Postava et al., 2015) and fewer depressive symptoms (Keyes et al., 2013) in OCP users vs. naturally-cycling women.

Two very large cohort studies reported higher rates of depression diagnoses, antidepressant prescriptions (Skovlund et al., 2016), and suicide (Skovlund et al., 2018) in OCP users vs. naturally-cycling women.

We performed a double-blind, placebo-controlled, randomized crossover trial testing effects of OCPs vs. placebo on mood and cortical thickness

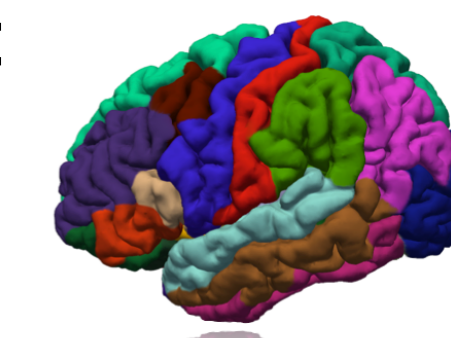


ELIGIBILITY: INTERVENTION: ANALYSIS: Freesurfer 6.0.0

Participants were required to have previous negative experience with OCPs

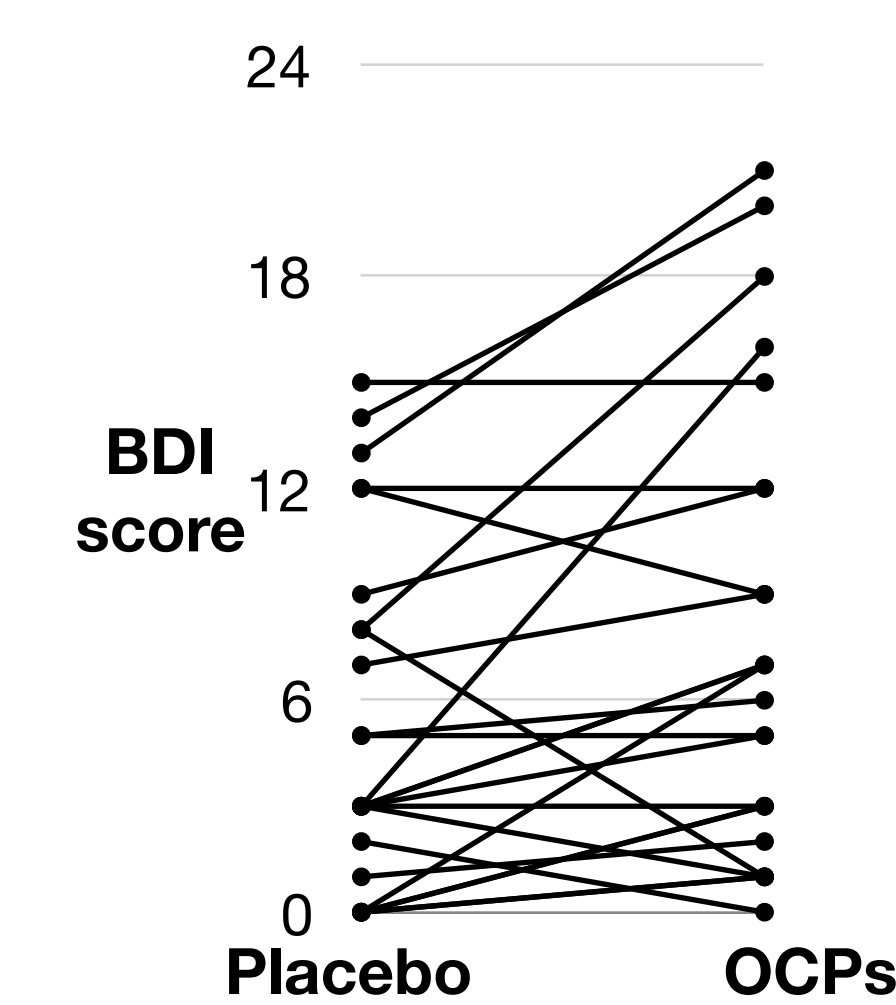
0.15 mg levonorgestrel + 0.30 μ g ethinyl estradiol for 18-21 days

ROIs: left and right caudal middle frontal, pars opercularis, pars orbitalis, pars triangularis, rostral middle frontal superior frontal, frontal pole, lateral orbitofrontal, medial orbitofrontal



Oral contraceptive pills increase negative mood symptoms

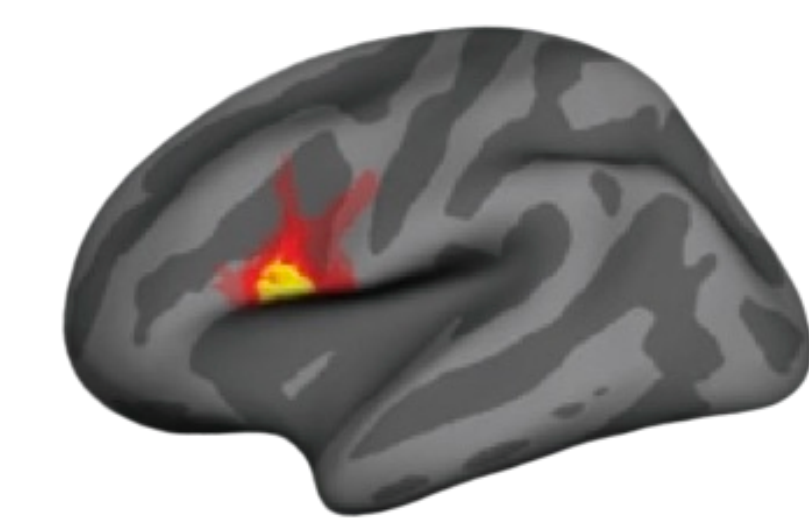
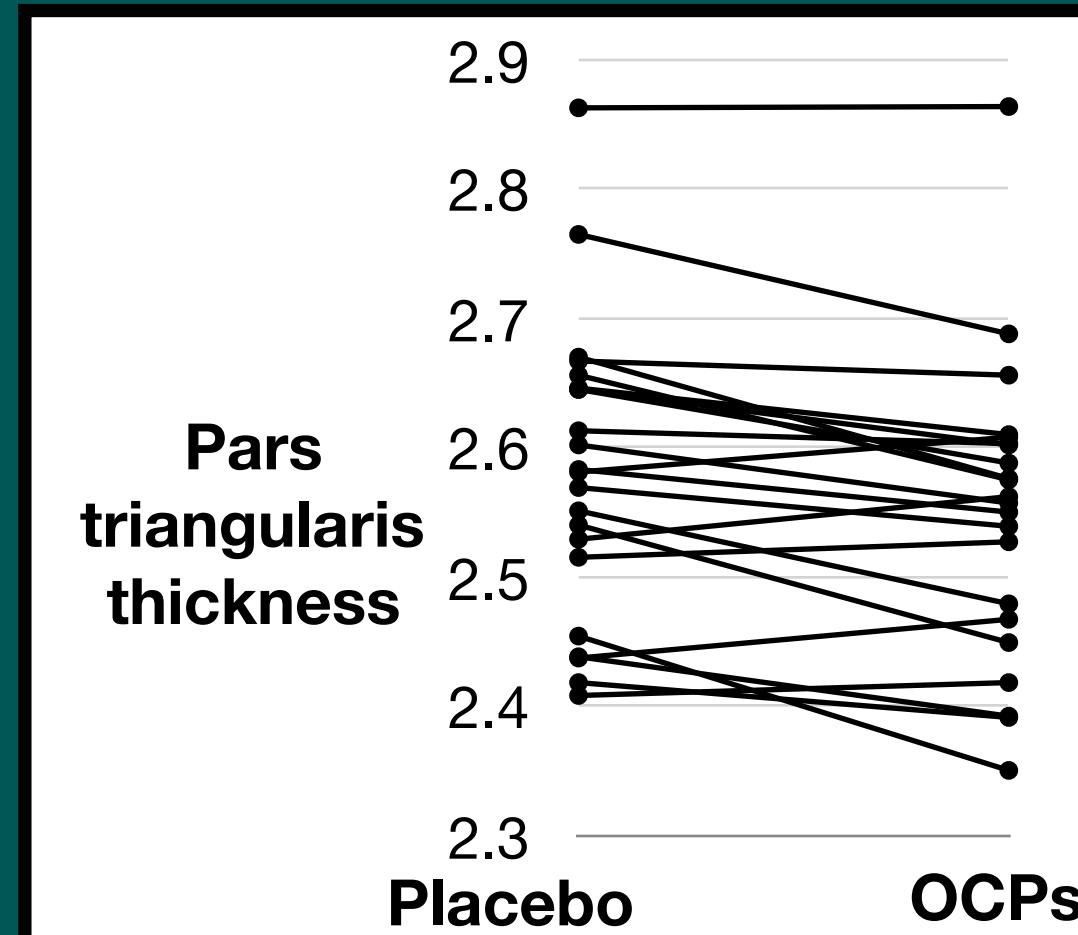
BDI score increased an average of 33%, from a mean of 5.68 to 7.56 ($p = 0.02$)



Daily Record of Severity of Problems

Symptom	p -value
Mood swings	$p = 0.04$ (OCP > PL)*
Physical	$p = 0.0005$ (OCP > PL)***
Productivity	$p = 0.02$ (OCP > PL)*
Social avoidance	$p = 0.03$ (OCP > PL)*

Oral contraceptive pills decrease right pars triangularis thickness



In all ROIs tested, cortical thickness was smaller during the OCP arm compared to the placebo arm. The difference was significant in at the $p < 0.05$ level in the left and right pars triangularis, right pars opercularis, and right frontal pole. The difference in the right pars triangularis ($p = 0.001$) survived familywise error correction.

A subset of women will experience emotional side effects and cortical thinning when using OCPs, and may be advised to discontinue them. Further studies are needed to prospectively identify these women.