have identified a functional polymorphism in close proximity of a GRE in intron 2 of *FKBP5*, which alters the extent of mRNA and protein induction following GR activation, likely by an altered 3D conformation. This results in a variable interaction of the intron 2 GRE with the transcription start site, leading to increased or reduced mRNA induction, respectively (Klengel *et al*, 2013). Individuals carrying the allele associated with stronger *FKBP5* mRNA induction show GR resistance, prolonged cortisol response following stress, altered activation of brain regions important for threat response, such as the amygdala, and increased risk to a number of psychiatric disorders including major depression and post-traumatic stress disorder when exposed to childhood trauma. Interestingly, while the genetic effects on the physiological stress response are seen in adults, no interaction of adult trauma with this genotype on psychiatric risk is observed, suggesting an additional mechanism that explains the *FKBP5* × childhood trauma interaction. In fact, we could show that exposure to childhood trauma leads to allele-specific epigenetic changes with a decrease in DNA methylation in a second GRE located in intron 7 of the gene, but only in carriers of the risk allele. This demethylation further de-represses *FKBP5* induction following GR exposure and is likely mediated by the genetically determined increase in cortisol response following stress (Klengel *et al*, 2013) (Figure 1). Indeed, direct GR activation with a selective agonist in a neuronal progenitor cell line leads to a demethylation in exactly the same CG dinucleotides (CpGs) that are shown to be less methylated in DNA from peripheral blood in trauma-exposed risk allele carriers. These CpGs are located either within or between GR consensus binding site sequences, while more proximal CpGs are unaffected. We thus speculate that the demethylation is an active demethylation, induced by GR binding. Such active demethylation at GREs has been described before (Kress *et al*, 2006) and, although not directly shown, hydroxymethylation could be an intermediate step in this active transcription factor binding-induced demethylation (Bhutani *et al*, 2011), a process that has been described for other transcription factors as well (Feldmann *et al*, 2013). On a more general level, any genetic variant that alters binding of stress-induced transcription factors may thus lead to local differences in subsequent epigenetic changes. Thereby, allele-specific epigenetic modifications can contribute to gene × environment interactions, leading to long-term effects of stress on endocrine levels, brain activity, and the risk to develop psychiatric disorders.

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Depression and Antidepressants in Pregnancy: Molecular and Psychosocial Mechanisms Affecting Offspring's Physical And Mental Health

A woman who is depressed in pregnancy faces the difficult process of weighting the pros and cons of starting antidepressant treatment, but unfortunately the evidence regarding the effects of antidepressants in pregnancy on offspring outcomes remains far from conclusive. At the same time, more studies are showing that untreated depression *per se* has negative consequences on offspring outcomes. Weighing the pros and cons in this context is by no means an easy process.

A number of population-based studies using prescriptions registers have found that treatment with antidepressants in pregnancy, especially with selective serotonin reuptake inhibitors, is associated with an increased risk of cardiac malformations (for exposure in the first trimester) and of pulmonary hypertension in the newborn (for exposure in the third trimester) (Pedersen *et al*, 2009; Grigoriadis *et al*, 2014). However, there is one main caveat: it is very difficult to distinguish the effects of antidepressants from the effects of untreated depression, as prescriptions registers often lack clinical information, and treatment allocation is not randomized. Even comparing the naturalistic cohorts of treated and untreated depressed women cannot adjust for the fact that treated women are likely to be more complex and more severely depressed—and therefore more likely to smoke, to drink alcohol, and to have less regular antenatal care. Indeed, one very recent study that has attempted to adjust for such variables using the US Medicaid database has found no substantial increase in the risk of cardiac malformations attributable to antidepressants (Huybrechts *et al*, 2014). Even

the (small) increase in pulmonary hypertension attributable to antidepressants could be explained by the higher risk of prematurity described in women who are depressed (Grigoriadis *et al*, 2014).

In the face of this recent, reassuring evidence about antidepressants' use in pregnancy, longitudinal studies are confirming the long-lasting adverse consequences of untreated depression in pregnancy for the emotional development of the offspring, and especially the increased risk of the offspring being exposed to maltreatment and bullying in childhood, and developing depression and antisocial behavior in adolescence and early adulthood (Pawlby *et al*, 2011; Pearson *et al*, 2013). These effects seem to be specific to depression during pregnancy, as they are not explained by the fact that these mothers tend to be depressed also postnatally: they thus implicate *in utero* 'biological programming' as one of the potential mechanisms. Indeed, stress and depression in pregnancy can affect the placental expression of enzymes regulating cortisol levels as well as offspring's stress response, methylation status of stress-related genes, and volume of the amygdala (Buss *et al*, 2012). Future studies should dissect the interaction between this complex constellation of factors, including depression in pregnancy (and its biological correlates, such as maternal cortisol and inflammation levels), infant stress-related behavior (again, with its biological correlates), mother–infant interaction, mother attachment, and offspring temperament.

Where do these studies leave the patients and the professionals? While starting an antidepressant in pregnancy may be perceived as 'an action', carrying moral responsibility (and liability), the alternative 'no action' of leaving a depressed woman untreated may harm the offspring through exposure to toxic life styles and an abnormal *in utero* biology. While non-pharmacological treatments may work in these women (for example, interpersonal psychotherapy, exercise, or omega-3 fatty acids), antidepressants will likely remain the mainstream option for moderate to severe depression in pregnancy (unless electroconvulsive therapy is required, a safe option in the most difficult cases). 'Not to treat' is no longer the safest choice.

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Which Is the Driver, the Obsessions or the Compulsions, in OCD?

The conventional view is that obsessive–compulsive disorder (OCD) is driven by irrational beliefs, which are a putative basis of obsessions. Compulsions are considered a coping mechanism, which neutralize anxiety or reduce the likelihood that these fears will be realized. Contrary to this view, recent data suggest that compulsions in OCD are a manifestation of a disruption in the neurobiologically well-defined balance between goal-directed action and automatic habits.

In one study, OCD patients and matched control subjects were trained to make simple instrumental responses to gain valuable outcomes (Gillan *et al*, 2011). Analogous to the 'outcome devaluation' technique developed to test for habits in rodents (Adams, 1980), these outcomes were then devalued by instructing the participant they were no longer worth points. If behavior is under goal-directed control, subjects should not make responses that yield devalued outcomes. Habits are reciprocally defined as automatic responses to stimuli that continue in spite of devaluation. Using this well-validated procedure, OCD patients demonstrated greater habits compared to healthy controls (Figure 1a). This result was replicated in the aversive domain, where patients were instead required to avoid an unpleasant shock to their wrists (Gillan *et al*, 2014a). These data suggest that the tendency towards developing compulsive-like habits in OCD is both valence independent and, as the content of the tasks employed were unrelated to OCD symptomatology, obsession independent. Together these data suggest that if excessive habit learning is an adequate model of compulsive behavior, then compulsions are not epiphenomenal, but rather constitute a core component of OCD.

The habit hypothesis of OCD is neurobiologically plausible; goal-directed control (which protects against habits) relies upon the integrity of two key brain regions implicated in the pathophysiology of OCD, the caudate nucleus and medial orbitofrontal cortex (Gillan *et al*, 2014). Neurobiological models of obsessions, on the other hand, are lacking. One promising model implies that obsessions may be a consequence of dysfunction in fear conditioning processes in OCD, whereby patients cannot adequately