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

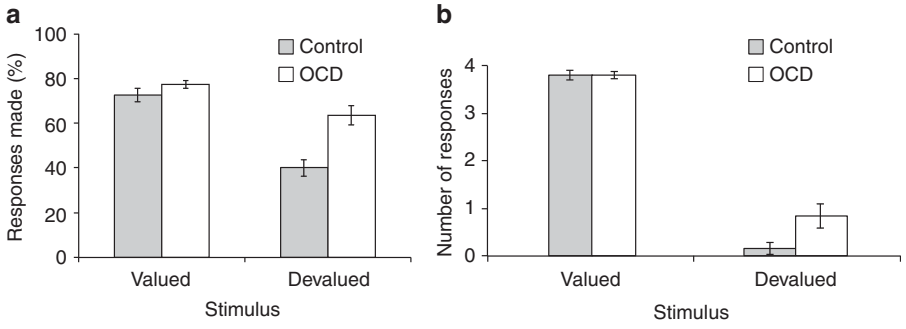

Figure 1. Excessive habit learning in OCD. Data reprinted with permission from Gillan *et al* (2011, 2014a). (a) OCD patients show excessive habit learning index by way of elevated responses towards devalued outcomes following appetitive instrumental learning. There was no group difference in responding for valuable outcomes (Gillan *et al*, 2011). (b) Over-active habits are also observed following aversive learning in OCD (Gillan *et al*, 2014a). Error bars denote standard error of the mean.

extinguish fears that accompany normal intrusive thoughts and worries. In support of this, impairments in extinction recall are evident in OCD, and the respective neural correlates also overlap on regions thought to be involved in the disorder (Milad *et al*, 2013). However, patients with post-traumatic stress disorder (PTSD), for example, have similar deficits in fear-extinction recall, but do not typically present with obsessions. In this light, fear-conditioning abnormalities in OCD may more parsimoniously reflect concomitant anxiety in OCD, rather than obsessions.

If not a dysfunction in fear extinction, what are obsessions in OCD? One possibility is that they are not an underlying trait in OCD, but instead an agitated mental urgency, or cognitive instantiation of more abstract feelings of anxiety and compulsive urges. A more elaborated view is that obsessions in OCD might arise as a result of compulsive behaviour. When trying to explain their bad habits, in the avoidance habit study described above, some OCD patients fell foul of reverse inference, erroneously deducing that if they felt driven to perform an act of (habitual) avoidance, they must have had something to fear (Gillan *et al*, 2014a). Studies have shown that with continued avoidance normal, albeit faulty, beliefs about threat cannot extinguish (Lovibond *et al*, 2009). It is plausible in this light that we have been thinking about OCD backwards: perhaps compulsions are a core feature of the disorder and obsessions are a troublesome by-product.

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Induced Pluripotent Stem Cell (iPSC) Models of Bipolar Disorder

Bipolar disorder (BP) is a progressive, life-threatening condition characterized by alternating episodes of severe depression and mania, ranked by the WHO as among the leading causes of lifetime disability. The heritability of BP is estimated at 85–95%, and genetic susceptibility loci, each with small effects, are emerging. Accumulating evidence suggests a developmental origin for BP: neuroanatomical abnormalities are often present at the first episode; there are organizational and neuronal migration alterations, with minimal astrogliosis. In addition, BP is typically diagnosed at adolescence when there is a shift from relying on earlier-developing brain regions to later-maturing prefrontal structures—a period when the brain may be particularly vulnerable to pre-existing neuropathologies (Strakowski, 2012). Since subtle changes in differentiation can produce neurological consequences that only become apparent much later in life, a developmental model to study BP is required.

The ability to reprogram adult somatic cells to induced pluripotent stem cells (iPSC) by expressing four transcription