on infant socio-emotional development (Rilling and Young, 2014). Preclinical studies suggest that OT increases the salience and rewarding value of social stimuli. OT acts in the rodent amygdala to enhance the salience of social olfactory cues. thereby facilitating social recognition, in the striatum to mediate social reward and in the hippocampus to enhance signal to noise neurotransmission. These fundamental processes likely contribute to more complex OT-mediated behaviors, including social bonding.

The effects of OT on social information processing in rodents make it an enticing pharmacological target for enhancing social cognition. However, two issues introduce skepticism for translating the compelling preclinical observations into effective pharmacotherapies to improve social functioning in psychiatric disorders, including autism and schizophrenia: (1) rodents use olfaction as the primary social perception modality, while primates rely more on visual and auditory social perception; (2) little is known regarding the pharmacokinetics of current OT administration methods or the impact of chronic OT treatment. Recent studies from our laboratory address these issues.

A common polymorphism in the human OT receptor (OXTR) gene predicts face recognition skills in families with a child with autism. This effect was present in all family members in two independent populations, yet there was no evidence of an association with autism diagnosis (Skuse *et al*, 2014). This study supports a role for the OT system in human visual social information processing analogous to its role in olfactory processing in rodents.

Nonhuman primates are useful for exploring the mechanisms of intranasal OT (IN-OT) administration. We showed that OT administered nasally by a pediatric nebulizer modestly elevates OT in the cerebrospinal fluid of anesthetized macaques (Modi *et al*, 2014). Importantly, intranasal OT also robustly elevated plasma OT for an extended period of time. Thus IN-OT may increase brain OT signaling, but peripheral mechanisms should be considered.

Comparative studies of brain OXTR distribution in primates reveal the potential mechanisms by which OT modulates social information processing (Freeman *et al*, 2014a, b). In all primate species examined, OXTRs are concentrated in cholinergic regions involved in visual and auditory processing, including the nucleus basalis of Meynert, which coordinates neural activity in the amygdala and cortex, thereby modulating attention to visual cues.

IN-OT may enhance some aspects of social cognition through the mechanisms described above, but the efficacy may be limited by brain penetration. Stimulating endogenous central OT release pharmacologically is a viable alternative for increasing OT neural signaling. Melanocortin receptor agonists stimulate OT release from hypothalamic slices, potentiate OT release in the ventral striatum, and enhance OT-dependent behavior in prairie voles (unpublished data). Neonatal melanocortin receptor activation acutely activates OT neurons, and daily treatment for the first week of life enhances adult social bonding in prairie voles (Barrett *et al*, 2014). Thus, the OT system remains an attractive target for clinically enhancing social cognition, and alternative pharmacological strategies for enhancing OT neurotransmission should be explored.

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FUNDING AND DISCLOSURE
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FKBP5 Allele-Specific Epigenetic Modification in Gene by Environment Interaction

The likelihood to develop stress-related psychiatric disorders in response to childhood trauma exposure may be moderated by the individual's genetic predisposition (Manuck and McCaffery, 2014). One of the genetic variants reported to alter the risk for psychiatric disorders following childhood trauma is a functional variant in *FKBP5*, a gene encoding a co-chaperone of the glucocorticoid receptor (GR). *FKBP5* is strongly induced following stress exposure via binding of activated GR to a number of intronic and promoter GR response elements (GREs). The protein itself then binds to the GR complex, reduces the affinity of GR to cortisol and decreases translocation of the GR to the nucleus, providing an ultrashort negative feedback for GR activation on the genomic and protein level (Zannas and Binder, 2014). We

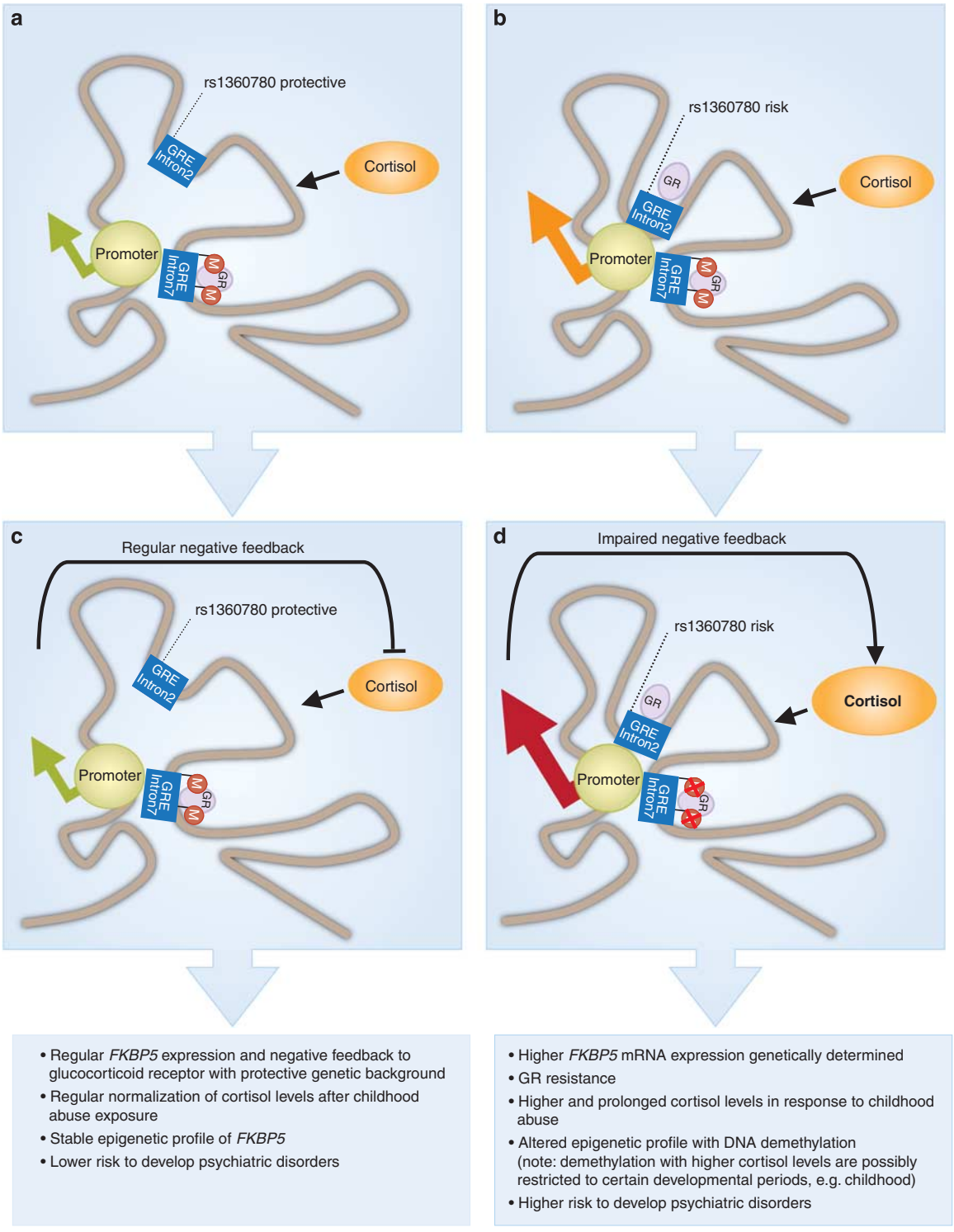

Figure 1. Schematic representation of an allele-specific epigenetic modification in *FKBP5*. The single-nucleotide polymorphism rs1360780 close to a functional GRE in intron 2 constitutes the genetic predisposition to an increased *FKBP5* transcriptional response to stress (a, b). (a) The C-allele of rs1360780 leads to an impaired binding of the intron 2 GRE to the promoter site. (b) In contrast, the T-allele of rs1360780 facilitates the binding of the intron 2 GRE to the promoter in response to GR activation, leading to an increased transcriptional response of *FKBP5*. When exposed to childhood abuse, the genetic predisposition facilitates the epigenetic response to trauma in *FKBP5* (c, d). (c) In carriers of the protective genotype, the exposure to childhood abuse leads to a regular transcriptional activation of *FKBP5* with a negative feedback of FKBP5 to the GR terminating the stress response after the end of the threat. The DNA methylation profile in protective genotype carriers remains stable. (d) In carriers of the risk allele, the exposure to childhood trauma leads to an increased activation of *FKBP5*, an impaired negative feedback to the GR and high cortisol levels over time. This leads to a reduction of DNA methylation in and around the intron 7 GRE, with an even stronger transcriptional activation in risk allele carriers. This de-repression of *FKBP5* in risk allele carriers leads to a GR resistance and increases the risk to develop stress-related psychiatric disorders.

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