Title: The role of genetic variation in the glucocorticoid receptor (NR3C1) and mineralocorticoid receptor (NR3C2) in the association between cortisol response and cognition under acute stress

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<AT>The role of genetic variation in the glucocorticoid receptor (NR3C1) and mineralocorticoid receptor (NR3C2) in the association between cortisol response and cognition under acute stress.
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<ABS-HEAD>Highlights► The effect of GR polymorphisms (including rs41423247) on HPA – axis reactivity is replicated ► An interaction of MR polymorphisms and cortisol reactivity following acute stress on attentional performance is shown ► Further individual factors contributing to the association between stress and cognition should be considered in the future

<ABS-HEAD>ABSTRACT

<ABS-P>Although HPA – axis reactivity has repeatedly been related to cognitive functioning, ambiguity remains regarding the direction of the effect, i.e. whether it benefits or impairs functioning. Genetic factors that contribute to HPA – axis reactivity on the one hand and to cognitive functioning on the other could therefore help clarify the association between stress and cognition. We genotyped 10 single nucleotide polymorphisms (SNPs) on the NR3C1 gene (rs10482682, rs33389, rs10482633, rs10515522, rs2963156, rs4128428, rs9324918, rs41423247, rs6189, rs10052957) coding for the glucocorticoid receptor (GR) and 4 SNPs on the NR3C2 gene (rs6810951, rs4635799, rs11099695, rs2070950) coding for the mineralocorticoid receptor (MR) and required *N*=126 healthy males to perform tasks assessing attention and reasoning before and after experiencing an acute laboratory stressor (the *Socially Evaluated Cold Pressor Test, SECPT*). Haplotype analyses revealed significant effects of NR3C1 ($p = .011$) and NR3C2 ($p = .034$) on cortisol stress response. NR3C2 also influenced attentional performance via an interaction with stress-induced cortisol response ($p < .001$). Neither NR3C1 haplotype nor NR3C2 haplotype was associated with reasoning abilities.
<ABS-P><ST>Results</ST> suggest that the association between stress induced cortisol reactivity and cognition strongly depends on genetic variation. The idea of an optimal arousal level depending on stress reactivity and genetic disposition is discussed.
<KWD>Keywords: NR3C1; NR3C2; cortisol; acute stress; cognitive functioning; attention

<H1>1. Introduction
The Hypothalamic Pituitary Adrenal (HPA) axis is an important endocrine modulator of the stress reaction that helps us cope with everyday challenges. Consequently, a dysregulation of the HPA - axis or – more specifically – a disruption of the cortisol homeostasis leads to an impairment in dealing with stressors. Therefore, abnormalities in HPA activity have repeatedly been associated with affective psychopathologies, most prominently depression (De Rijk et al., 2008; Gold, Licinio, Wong & Chrousos, 1995; Stetler & Miller, 2011). A large number of studies show altered cortisol levels in depressed patients following acute stress (Pariante & Lightman, 2008), as well as slower recovery from stress (Burke et al., 2005) and altered tonic cortisol levels, both after waking (Chida & Steptoe, 2009; Fries, Dettenbom, & Kirschbaum, 2009) and over the course of the day (van den Bergh et al., 2008). Several explanations have been posited to account for the relationship between disrupted HPA axis functioning and depression. Some studies suggest an effect of adverse life events in childhood on cortisol levels in adulthood (McCrory, De Brito & Viding, 2011). Genetic variance may also explain the relationship between depression and the HPA-axis. The NR3C1