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Chapter 6

General Discussion
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Aim of the dissertation

The aim of this dissertation was to investigate the antidepressant properties of two compounds: a novel compound, ARA290, and a well-known compound, L-tryptophan.

ARA290 is a relatively new compound and studies on its effects on cognition and behaviour in healthy individuals are sparse. We used a neuropsychological model of drug action (Harmer et al., 2009) to test its possible antidepressant effects in healthy volunteers. As summarized in the introduction, this model has been validated with registered antidepressants and is based on the finding that single dose or short term (1 week) administration of antidepressants in healthy volunteers results in a shift towards a more positive bias in various domains of emotional information processing such as attention, memory and recognition of facial expressions (Harmer et al., 2011). This early shift in emotional information processing may also be reflected in physiological (startle response) and neural changes (BOLD response) in healthy volunteers (Harmer et al., 2011). In sum, the validated neuropsychological model of drug action includes behavioural, psychological and neural measures that can be applied in order to detect early antidepressant-like effects of new compounds in healthy volunteers. It is suggested that this model provides an early indication of how promising/efficient a new compound may eventually be in clinical populations (Harmer et al., 2009; Harmer et al., 2011). In addition to the primary outcomes of the neuropsychological model of drug action, which tap into emotional information processing, we also included resting-state fMRI as a measure in order to investigate the effects of ARA290 on resting-state connectivity.

Next to a new compound ARA290, we also investigated the antidepressant properties of a better-known compound, L-tryptophan which has been investigated as an add-on compound to conventional antidepressants (Coppen et al., 1963; 1972). Since the effect of tryptophan manipulations on social-emotional information processing in healthy populations is relatively well known (Moskowitz et al., 2001; Aan het Rot et al., 2006; 2010), we aimed to further investigate the antidepressant effects of L-tryptophan by testing its effects in a healthy population possessing a genetic marker (serotonin transporter polymorphism) that is linked to depression vulnerability.

In order to assess the potential therapeutic effects of L-tryptophan, a selection of measures were applied. These measures include comparable behavioural and physiological vulnerability markers as those included in the neuropsychological model of drug action. The selection was based on recent studies on the effects of serotonin manipulations on cognition. Specifically, social-emotional decision making (behavioural) and stress or HPA-axis reactivity (physiological) were investigated.

The assessment of neuropsychological effects of interventions in healthy individuals has the advantage that they do not have a current disorder or a history of psychiatric disorders and that
their cognitive performances are not ‘contaminated’ by earlier pharmacological treatment. The idea is that vulnerability markers of depression are also present to varying degrees in healthy individuals who do not have a history of depression. The neuropsychological effects of ARA290 and tryptophan in healthy individuals were assessed by comparing placebo and intervention groups who had not had earlier treatment.

1a. Does ARA290, a novel pharmacological compound, have antidepressant effects?

Although a single dose of ARA290 (i.v. 2 mg) in healthy individuals did show an effect on some measures of the neuropsychological model of drug action, the effects were small and not all of these were in the expected direction of an antidepressant effect. Specifically, ARA290-treated individuals had smaller neural responses to happy faces in the fusiform gyrus, but no neural differences during the memory task. Furthermore, ARA-290 was not associated with changes in the functional connectivity of the brain. At the behavioural level, ARA290 had no effect on the recognition of emotions in facial expressions. ARA290 did have an effect on the categorization of self-referential words as ARA290 was associated with faster categorization of positive vs negative words, but not with a better memory for positive words. Furthermore, ARA290 was associated with a higher positive attentional bias score than placebo. No effects of ARA290 were observed on measures of mood and psychiatric symptoms. Taken together, these findings suggest that a single administration of ARA290 elicited the expected shift from positive to a negative bias on two measures of the emotional test battery. These were not the primary outcome measures, however – these outcome measures are a part of the emotional test battery and are based on previous effects of registered antidepressants or EPO. Furthermore, since we had no baseline assessments, it cannot be excluded that the effects represent pre-existing group differences.

1b. Effects of ARA290 - Limitations

Developed as an analogue of EPO, ARA290 is a peptide consisting of 11-amino acids which acts on the Innate Repair Receptor (IRR). The IRR consist of a β-common receptor (BCR) subunit (CD131) coupled to an EPO receptor (EPOR) and its activation initiates signalling pathways that mediate tissue protection, without initiating hematopoietic effects (Review, Brines and Cerami, 2012). Considering a) the tissue protective and anti-inflammatory role of ARA290 in animals and humans (Pulman et al., 2013; Dahan et al., 2013), b) the beneficial effects on cognitive performance in chronic schizophrenic patients (Ehrenreich et al., 2007b) and c) the antidepressant-like effects of EPO in healthy individuals (Miskowiak et al., 2007a; 2007b), we sought to answer the question of whether ARA290 exerts similar antidepressant-like effects as EPO does. Since EPO was tested with the neuropsychological model of drug action, we applied the same model and experimental design (incl. frequency of ARA290 administration and timing of testing).
The absence of distinct antidepressant-like effects in our study may be due to differences in pharmacokinetics between EPO and ARA290. In humans, EPO has an elimination half-life of approximately 5 hours (Eckardt et al., 1989; McMahon et al., 1990), whereas ARA290 has an elimination half-life of approximately 2 minutes following i.v. administration (Niesters et al., 2013). Despite the short elimination half-life, ARA290 is suggested to pass rapidly into the CNS and elicit durable effects due to the activation of IRR which regulates the innate tissue-protective response in various stages over a period from hours to days (Brines et al., 2008a; Brines and Cerami, 2012). Consistent with this, a phase 1 study in patients suffering from sarcoidosis or diabetes-induced neuropathy showed that ARA290 (i.v. 2 mg) administration for 3 days (spread over one week) reduced pain scores; an effect that lasted for 3 days following the last treatment (Niesters et al., 2013). Furthermore, first phase human studies with ARA290 indicated modest improvements in cognitive measures six hours after a single dose (Investigators brochure ARA290, 2009). Since first phase studies in humans did not raise safety concerns with the dose of 2 mg i.v. administration, we chose to administer the same dosage in our study. The time interval of measuring the antidepressant effects of ARA290 was chosen based on the studies investigating the antidepressant effects of EPO by means of the neuropsychological model of drug action (i.e., 6-7 days post administration). It is, therefore, conceivable that we have missed some effects of ARA290 on emotional information processing and cognition in general due to 1) possibly incorrect timing of measurement and 2) possibly ineffective dose of ARA290. An explanation for the lack of distinct antidepressant-like effects may be that either the timing of measurements should have been shorter after a single dose of administration (e.g., 2-3 days post administration) and/or that the dose of ARA290 administration should have been higher or that repeated administration (e.g., three administrations of 2 mg spread over a week) is needed in order to produce detectable effects at cognitive level.

Besides the differences in pharmacokinetics between EPO and ARA290, some limitations of the neuropsychological model also need to be addressed. The behavioural measures included in the test battery tap into different aspects of emotional information processing such as attention, memory and recognition of emotional facial expressions. Most of the stimuli used in these behavioural measures have an emotional content and are subject to habituation as well as learning effects. The majority of the tests included in the battery of emotional information processing can therefore be administered only once. Due to this restriction we chose not to take baseline measurements prior to the pharmacological intervention. In order to compensate for the lack of baseline measurements we increased the number of participants in our study (N=36). This is higher than the fMRI studies on EPO in healthy participants (N= 24) (Miskowiak et al., 2007a), that also had no baseline assessments. Baseline measures would of course have provided objective measures of inter-subject variability and differences in response between groups prior to intervention.

Another possible point of criticism relates to the design of the cognitive challenges during fMRI scanning, which are a part of the neuropsychological model. To facilitate comparison
with prior research, the fMRI tasks in our study were presented in a block-design. Therefore, it is conceivable that we did not observe distinct differences in hippocampal function between groups during the picture recognition task as a block-design limits the possibility to analyse responses to individual trials. Presentation of trials in an event-related design would have made it possible to investigate the changes in hemodynamic response during correct and incorrect recognition of pictures. In a block-design, however, it is not possible to distinguish between correct vs. incorrect recognition. Consequently, changes in BOLD response associated with correct and incorrect recognition could not be modelled in the data.

Overall, the effects of ARA290 on the neural response during task performance are task specific rather than a general effect of ARA290 on these regions, as ARA290 was not associated with changes in the functional connectivity of the brain.

**1c. Effects of ARA290 – Underlying biological mechanism**

Although ARA290 seems to elicit changes in a few domains of emotional information processing, overall the results indicate that a single administration of ARA290 is not sufficient to initiate the explicit shift towards a more positive bias in emotional information processing as had been hypothesized based on the neuropsychological model we have applied. Possible limitations of our studies are discussed in paragraph 1b, however, the question that needs to be answered at this point is a) whether it is worthwhile to continue to study ARA290 as a therapeutic compound for depression, and if so b) which steps are needed in order to further investigate the potential of ARA290 as antidepressant drug.

Our findings with a single administration of ARA290 in healthy individuals does not seem particularly promising as an antidepressant compound, however, when taking into consideration the positive findings reported in clinical trials with patients suffering from peripheral neuropathy together with the cellular pathways activated by ARA290, the antidepressant-like effects of ARA290 may need to be explored with a different approach.

ARA290 activates the IRR, a receptor which is locally up-regulated following tissue damage (Brines and Cerami, 2008b). In the brain, activation of the IRR leads to the activation of the STAT pathway (Fu et al., 2010; Brines and Cerami, 2012) which in turn results in the up-regulation of survival signals and the inhibition of inflammation-induced apoptosis (Brines and Cerami, 2012). Furthermore, activation of the STAT3 and STAT5 pathways in human neural stem cells facilitate the differentiation of neural stem cells and outgrowth of neurites (Fu et al., 2010). In rodents, ARA290 suppresses the inflammation response in spinal microglia following nerve injury providing evidence for central anti-inflammatory actions of ARA290 (Swartjes et al., 2014). Also, phase 1 and 2 clinical trials in neuropathy patients indicate beneficial effects of ARA290 on pain symptoms (Nieters et al., 2013; van Velzen et al., 2014) which are suggested to be mediated by the anti-inflammatory and tissue restorative actions initiated by ARA290 (van Velzen et al., 2014). Given these aforementioned findings, it
is conceivable that antidepressant-like effects of ARA290 occur and/or are only detectable in the “appropriate” biological environment, i.e. in individuals with increased levels of inflammatory biomarkers (i.e. elevated levels of pro-inflammatory cytokines). Inflammation has been proposed as one of the biological mechanisms underlying depression and has been recognized as a biological factor increasing the risk to develop MDD (as reviewed by Dantzer et al., 2008; Rosenblat et al., 2014), it is therefore possible that ARA290 exerts antidepressant-like effects in a subgroup of individuals who are vulnerable to develop depression due to the presence of high inflammation bio-markers. Besides the limitations discussed in section 1b concerning proper timing of assessment following ARA290 administration, future studies would also benefit from examining the effect of ARA290 on depressive symptoms (e.g., fatigue, sleep disturbances, changes in appetite, mood and cognition) in biologically vulnerable populations (i.e., individuals who are at risk to develop MDD due to conditions of high inflammation).

2a. Does L-tryptophan, a dietary compound, have antidepressant effects?

The effect of prolonged (six days) intake of TRP on HPA-axis reactivity (cortisol response) and social decision making (response to unfairness) was examined in a sample selected on genotype (i.e., S'/S' and L'/L' carriers of the 5-HTTLPR genotype). Our results indicate that TRP supplementation lowers the cortisol response to social stress in S'/S' carriers of the serotonin transporter gene while it has no effect on the cortisol response in L'/L' carriers. TRP supplementation for six days had no effect on mood or on symptoms of anxiety and depression in either of the genotype groups. The same study indicates that TRP supplementation does not influence the behavioural response to unfairness in the ultimatum game (UG). A non-significant difference was found in the opposite direction as expected: the tryptophan-group had higher rejection rates of very unfair offers than the placebo group. Also, 5-HTTLPR genotype did not influence the behavioural response to unfairness.

2b. Effects of L-tryptophan – Limitations

The beneficial effects of tryptophan on stress response in healthy volunteers appears to be specific for a certain genotype, i.e., the S'/S' variant of the 5-HTTLPR. Tryptophan did not have an effect on social decision making in either (L'/L' or S'/S') variant of the 5-HTTLPR genotype.

The response to unfairness in the ultimatum game in healthy subjects appears to be under serotonergic control as acute tryptophan depletion was associated with a higher rejection rate of very unfair offers (Crockett et al., 2008), whereas a single dose of the selective serotonin reuptake inhibitor (SSRI) citalopram (30 mg) was associated with a lower rejection rate of unfair offers (Crockett et al., 2010). Our study showed that tryptophan supplementation for six days did not modulate the response to unfairness in the Ultimatum game. At day 7 the
TRP group seemed to reject very unfair offers more often if the stakes were relatively high, which is in the opposite direction as expected based on the findings of Crockett et al. (2010). However, the effect was a non-significant in our study. S'/S' carriers of the 5-HTTPLR were expected to reject more offers (regardless the of level of unfairness) prior to treatment and were expected to benefit from the TRP supplementation in order to make more utilitarian decisions by lower rejection rates of unfair offers. However, 5-HTTPLR genotype did not influence the response to unfair offers.

In our study we did not draw blood samples pre- and post TRP supplementation to prevent possible interference with the cortisol response to the stress induction (i.e. Trier Social Stress Task). Although plasma TRP is an indirect measure of central serotonin availability, the lack of TRP plasma ratios pre- and post TRP supplementation complicates the interpretation of the null findings. Several possibilities could have been excluded if we would have measured plasma TRP levels. The last TRP intake was on the evening of the 6th day and the UG was performed on day 7. This may have turned our intended TRP supplementation into a relative depletion of TRP compared to the six days of supplementation prior to the day of testing. Oral TRP administration 50 mg/kg (3.5 g for 70 kg – mixed in milk) to humans showed that TRP concentration in blood reaches a peak approx. after 6 hours and returns to its baseline value after 12 hours, whereas, in the cerebrospinal fluid the peak is reached earlier (between six and ten hours) and returns to baseline after approx. 18 hours (Eccleston et al., 1970). This early study of Eccleston et al. (1970) was carried out with a small sample size and needs to be interpreted with caution. However, even if a relative depletion was caused by the interruption of TRP supplementation at the day of testing, this may have pushed TRP levels back to baseline but would not cause the sizeable drop in TRP concentrations that is reached with an ATD procedure (i.e., approx. 70-90% drop from baseline, see review Van der Does, 2001). In addition, the effect we expected from prolonged TRP supplementation on ultimatum game behaviour was based on the idea of the cognitive neuropsychological model of Harmer et al. (2009) which hypothesizes that the neuro-adaptive effects of antidepressant agents, together with social interactions occur in parallel and reshape emotional biases which lead to a shift from negative to positive biases. In line with this hypothesis, TRP supplementation was expected to lead to a positive switch in which participants would be able to override their negative emotion towards unfair offers and would be able to make utilitarian decisions. Furthermore, at the same day of testing (i.e., day 7) we still observed an effect of TRP supplementation on the cortisol response to social stress in S'/S' carriers. Perhaps, in contrast to HPA-axis reactivity, social decision making and social cognition in general is more dependent on absolute TRP levels (i.e. acute increase or decrease in TRP availability). The studies that have shown the effect of serotonin availability on social decision making were interventions in which the effect of manipulating serotonin availability (either by means of SSRI's, TRP loading or depletion) was measured quickly after (approx. 1-2 hours) a single administration (Crockett et al., 2008; 2010; Colzato et al., 2013).
Another possible methodological limitation may be the absence of dietary instructions on the day of testing itself (i.e., day 7). We asked participants to refrain from food intake 1 hour before arrival to the laboratory, however, more specific instructions (e.g. restricting protein rich food) regarding their food intake before arrival (i.e., for breakfast or lunch) to the laboratory may have been beneficial in order to control the possible drop in TRP availability to the brain due to competing amino acids.

Although we did find an effect of TRP supplementation on the cortisol response in S'/S' carriers, one could argue that our study was underpowered to detect genetic effects on social decision making as genetic studies require larger sample sizes (Review, Burmeister et al., 2008). Also, our parallel design, in combination with the number of participants may not have yielded enough power to replicate the pharmacological effects on the UG as Crockett et al. (2008) and Crockett et al. (2010) has found with a cross-over design, which has a larger statistical power.

Overall, our study may have benefitted from biological measures related to TRP metabolism. Although plasma TRP/LNAA ratio is a peripheral and indirect measure of TRP availability, plasma measures pre- and post-intervention a) would have given more insight in the possible explanation underlying the lack of behavioural effects on the UG following a 6-day TRP supplementation and b) would have revealed possible non-compliance, although the latter being very unlikely given the findings on the physiological level (Cerit et al. 2013).

2c. Effects of L-tryptophan – Underlying biological mechanism

The effects of tryptophan are rather well known as most of the early studies have investigated its additive antidepressant effects in combination with conventional antidepressant drugs or with electroconvulsive therapy (Coppen et al., 1963; 1967; 1972; D'Elia et al., 1977a,b; Møller et al., 1980). Although research on the antidepressant properties of tryptophan has diminished due to the introduction of SSRIs (Parker and Brotchie, 2011), the effects of increasing serotonin availability on emotional information processing and mood are relatively well documented (Booij et al., 2006; aan het Rot et al., 2006). Therefore, in contrast to our ARA290 study - in which we directly applied the neuropsychological model of drug action in order to examine its antidepressant effects for the first time in healthy individuals - in the tryptophan study we included alternative measures in order to examine the beneficial effects of tryptophan in healthy individuals. Social decision making and HPA-axis reactivity were of special interest as both measures have been shown to be sensitive to serotonergic manipulations either induced by experimental interventions (TRP loading or depletion) or serotonergic antidepressants (Crockett et al., 2008; 2010; Markus and Firk, 2009).

Tryptophan supplementation lowered the cortisol response to acute stress in S'/S'-carriers. The involvement of the serotonin system in the control of the HPA axis during an acute stress response is complex and remains a subject of study in both humans and animals (Markus
The generally accepted view is that the serotonergic system is not an unitary system and has a stimulating as well as an inhibiting role in the regulation of a stress response (McAllister – Williams et al., 1998; Markus et al., 2000). The stimulatory effect of serotonin on the HPA-axis activity is mediated through 5HT1A and 5HT2a and 5-HT2c receptors in the hypothalamic paraventricular nucleus and the pituitary (McAllister – Williams et al., 1998; Lowry, 2002), while the inhibiting effect of serotonin is mediated through 5-HT1A receptors in the hippocampus where serotonin exerts negative feedback control over the HPA axis (McAllister – Williams et al., 1998; Markus et al., 2000). Although the exact mechanism of the serotonergic control over the HPA axis is unclear, an imbalance/disturbance in the interaction between the two systems results in an inadequate biological response to stressful situations making it difficult to cope with stress (Markus et al., 2000).

Sufficient serotonergic activity during stressful situations is thought to be essential for an adequate biological response and stress adaptation (Markus et al., 2000). Based on this premise Markus et al., (2000) hypothesized that stress-prone individuals, defined as having high neuroticism scores, are subject to a constant lack of serotonin availability due to chronic stress exposure, and consequently, possess a hypersensitive serotonergic system. Stress-prone individuals with a hypersensitive serotonergic system are therefore expected to benefit from a diet that increases the TRP/LNAA ratios, and presumably central serotonin. Such diet would also result in a normalized HPA-axis activity/stress response, as indexed by a reduced cortisol response when exposed to acute stress (Markus et al., 2000). The authors suggested two possible mechanisms of how increased serotonergic activity in stress-prone individuals may be involved in the control of the HPA-axis (i.e. reduced cortisol response): 1) Increasing serotonin availability may act on the serotonergic innervations of the hippocampus by the median raphe nucleus. It is known that serotonin in the hippocampus exerts negative feedback control over the HPA axis (Jacobson 1991; Markus 2000). Hippocampi with higher serotonergic sensitivity, as assumed to be the case in stress-prone individuals, may exert a stronger negative feedback on the HPA axis following increased TRP availability. As a result of this, a reduction of cortisol release will follow due to more pronounced inhibiting action of serotonin. 2) Increasing serotonin availability may lead to enhanced activation of higher cortical structures such as the prefrontal cortex, thereby increasing their control over limbic adreno-cortical system (Markus et al., 2000).

Although these proposed underlying mechanisms remain speculative, the short variant of the 5-HTTLPR is associated with less serotonin uptake activity, leaving more serotonin in the synaptic cleft compared to the long variant. The 5HT1A auto-receptor is an important regulator in the serotonergic system and continuous stimulation of the 5HT1A receptor by 5HT in s/s carriers may decrease 5-HT synthesis and release resulting in shortage of 5-HT availability, similarly as has been shown for the mechanism of action of antidepressants (Blier and de Montigny, 1998). Assuming that the short allele carriers have a hypersensitive serotonergic system due to chronic shortage of serotonin availability (i.e. serotonergic activity is reduced by the inhibitory feedback of 5HT1A receptors), sub chronic administration of TRP
may have normalized the reduced serotonergic activity. The normalization of serotonergic activity, in either the serotonergic innervations of the hippocampus or enhanced higher cortical control over limbic adrenocortical structures, may have resulted in normalization of cortisol response in $S'/S'$ carriers of the 5-HTTLPR genotype.

The underlying neural mechanism of the sensitivity to acute stress in $S'/S'$ carriers of the 5-HTTLPR has been investigated by applying unpredictable electric shocks in healthy women during fMRI scanning (Drabant et al., 2012). During anticipation to acute stress, $S'/S'$ carriers exhibited an enhanced activation in the amygdala, hippocampus, anterior insula, thalamus, pulvinar, caudate, precuneus, anterior cingulate cortex, and the medial prefrontal cortex (mPFC) compared to L'-allele carriers (Drabant et al., 2012). Although no increase of central serotonin availability was induced and no direct or indirect measures of HPA-axis were included, this study showed that brain structures involved in the processing of threat are more active during acute stress in $S'/S'$ carriers, possibly due to a lack of (serotonergic) control of higher cortical structures over these limbic subcortical structures.

While a large meta-analysis on the effect of 5-HTTLPR on antidepressant efficacy concluded that 5-HTTLPR does not predict antidepressant response in MDD patients (Taylor et al., 2010), another meta-analysis found that in Caucasians (but not in Asians), the L allele was associated with higher probability of response and remission when treated with SSRIs (Porcelli et al., 2012). The finding that L allele carriers are more responsive to SSRIs, seems to contradict with our finding that tryptophan supplementation did not have an effect on the cortisol response during stress in L-allele carriers, while it did attenuate the cortisol response in S-allele carriers. Our study was conducted in a Caucasian population and although both tryptophan and SSRIs influence serotonergic neurotransmission, they are different interventions. SSRIs act on the serotonin transporter in order to block the re-uptake of serotonin from the synaptic cleft, whereas tryptophan is a precursor of serotonin. Besides its role in the brain, tryptophan metabolism occurs in other tissues, and it contributes to various bodily functions including immune response and intestinal functions (Le Floc’h et al., 2011). Furthermore, the aforementioned meta-analyses have a focus on treatment response in patients, whereas our study has focussed specifically on the HPA axis reactivity as indexed by cortisol response to acute social stress in healthy individuals. These differences between the two interventions (antidepressant drugs and tryptophan) and the different focus of the meta-analysis (i.e. reduction of symptoms in patients), make it difficult to extrapolate the findings regarding 5-HTTLPR and SSRI efficacy to our study conducted with six days of tryptophan supplementation. In general our findings support the notion that variation of 5-HTTLPR genotype is associated with altered reactivity to serotonergic manipulations.

3. General Conclusion

The cognitive neuropsychological model has been proposed as a complementary tool to predict the efficacy of antidepressant compounds before the stage of large scale and
expensive RCTs (Harmer et al., 2009; 2011). The effects of ARA290 were small and not all of these were in the expected direction of an antidepressant-like effect. Future studies may benefit from repeated ARA290 administration over time, and/or a shorter period between administration of ARA290 and testing. Furthermore, regardless of the model applied, it is essential to take into account the “biological environment” in which the compound is expected to exert an effect. In the future ARA290, as an anti-inflammatory compound, may be administered to healthy but depression vulnerable individuals as determined by high inflammation biomarkers. The beneficial effects of ARA290 may be more distinct when tapped into a specific (biological) vulnerability factor (i.e. inflammatory conditions).

Tryptophan lowered the cortisol response to stress only in S'/S' carriers of the 5-HTTLPR genotype while it did not affect the L'/L', which indicates a beneficial, although not necessarily an antidepressant effect, of tryptophan in a specific genetically vulnerable group. The effect of tryptophan on social decision making was not modulated by 5-HTTLPR genotype. In the future the modulation of social decision making by 5-HTTLPR genotype may be investigated by means of acute interventions (i.e. acute increase in TRP availability) rather than prolonged interventions (i.e. six days).

The potential of (human) experimental medicine models in predicting antidepressant drug efficacy may be improved by a) defining system-specific biological vulnerability factors implicated in the aetiology of depression together with the selection of the population based on these biological vulnerability factors, and by b) targeting biomarkers specific to the defective process implemented in depression.
References


