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The many different faces of major depression: It is time for personalized medicine

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ABSTRACT

First line antidepressants are the so-called SSRIs (selective serotonin reuptake inhibitors), e.g. fluvoxamine, fluoxetine, sertraline, paroxetine and escitalopram. Unfortunately, these drugs mostly do not provide full symptom relief and have a slow onset of action. Therefore other antidepressants are also being prescribed that inhibit the reuptake of norepinephrine (e.g. reboxetine, desipramine) or the reuptake of both serotonin (5-HT) and norepinephrine (e.g. venlafaxine, duloxetine, milnacipran). Nevertheless, many patients encounter residual symptoms such as impaired pleasure, impaired motivation, and lack of energy. It is hypothesized that an impaired brain reward system may underlie these residual symptoms. In agreement, there is some evidence that reuptake inhibitors of both norepinephrine and dopamine (e.g. methylphenidate, bupropion, nomifensine) affect these residual symptoms. In the pipeline are new drugs that block all three monoamine transporters for the reuptake of 5-HT, norepinephrine and dopamine, the so-called triple reuptake inhibitors (TRI). The working mechanisms of the above-mentioned antidepressants are discussed, and it is speculated whether depressed patients with different symptoms, sometimes even opposite ones due to atypical or melancholic features, can be matched with the different drug treatments available. In other words, is personalized medicine for major depression an option in the near future?

1. Introduction

This contribution in the Festschrift for Berend Olivier is about antidepressant drugs and personalized medicine. Major depression destroys the life of many patients and their families. It is estimated that depression increases the risk of suicide by 20 times. Depression is one of the most prevalent mental disorders, affecting about 121 million people worldwide and is among the leading causes of disability. The World Health Organization (WHO) estimates that by the year 2020, depression will be the second most common cause of disease and premature death worldwide (Murray et al., 2014), and by 2030 depression will be the leading cause of disease burden in the world (Mathers and Loncar, 2006). Furthermore, depression is one of the most common reasons that people are absent from work, or are unable to run a home.

Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; CRF, corticotropin-releasing factor; HPA, hypothalamus-pituitary-adrenal; WHO, World Health Organization; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5; MOA, monoamine oxidase; VMAT, vesicular monoamine transporter; COMT, catechol-O-methyltransferase; TCA, tricyclic antidepressant; SERT, serotonin transporter; NET, norepinephrine transporter; DAT, dopamine transporter; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; NRI, norepinephrine reuptake inhibitor; DNRI, dopamine–norepinephrine reuptake inhibitor; TRI, triple reuptake inhibitor; PFC, prefrontal cortex; NAc, nucleus accumbens; LC, locus coeruleus; VTA, ventral tegmental area; BNST, bed nucleus of the stria terminalis; ICSS, intracranial self-stimulation; MCP-1, monocyte chemotactic protein-1; NMDA, N-methyl-D-aspartic acid

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1.1. The history of monoaminergic antidepressants

The history of antidepressants is one of serendipity. Not intended, but keen perception to link together apparently innocuous facts has lead to the first antidepressant drugs. In the 1950s a drug called iproniazid was developed for the treatment of tuberculosis. Being ineffective in treating tuberculosis, however, it was found to be effective in reducing depressive symptoms in some patients that were primarily suffering from tuberculosis or other infections/inflammations (Loomer et al., 1957). It was discovered that iproniazid worked by inhibiting the enzyme monoamine oxidase (MOA), which is located in a neuron's nerve terminals (Zeller and Barsky, 1952). The enzyme MAO is responsible for breaking down the excess release of monoamines, such as norepinephrine, dopamine and serotonin (5-HT). Thus, MAO-inhibitors (MAOIs) increase levels of synaptic monoamines in the brain. Consequently, it was postulated that major depression was associated with a decrease in synaptic activity of neural connections that employ monoamine neurotransmitters; or, in other words, reduced the levels of monoamine neurotransmitters in the brain. Interestingly, further support for this idea came, although not without controversy, from the observation that the drug reserpine produced depressive mood in patients (Kass and Brown, 1955). Reserpine irreversibly blocks the vesicular monoamine transporter (VMAT) (Henry and Scherman, 1989) and lowers monoamine levels in the brain, because free intracellular monoamines cannot be transported into the presynaptic vesicles for subsequent release into the synaptic cleft (Kopin, 1994). Although the first MAOIs were very effective, they were also problematic because of the strict diet people needed to follow to prevent toxic consequences and other side effects of the drug. Recent advancements in technology, however, may alleviate some of these safety issues for instance by administering MAO inhibitors (e.g. selegiline) transdermal (Stahl and Felker, 2008).

In 1956, the Swiss psychiatrist Ronald Kuhn tested a chlorpromazine-like product (now known as imipramine) in patients with schizophrenia. Kuhn saw in individual patients the potential of imipramine as an antidepressant, although it was not effective in schizophrenia. By the end of 1957 he had presented imipramine's positive effects on depressed mood in a larger patient cohort. The pharmaceutical company Ciba-Geigy brought imipramine onto the European market in the late 1950s and into the U.S. in 1960. Imipramine was the first tricyclic antidepressant (TCA). Called tricyclic because the molecular structure had three rings of atoms. Unfortunately, TCAs have many adverse side effects and are easily overdosed with possible life-threatening consequences. TCAs had become the WHO number-one recommended drug for major depression by the beginning of 1970.

Between 1958 and 1961, Julius Axelrod carried out experiments on the regulation of neurotransmitters that earned him the Nobel Prize in 1970. Axelrod discovered that monoamines in the brain are rapidly metabolized by the enzyme catechol-O-methyltransferase (COMT) in the brain (Axelrod and Tomchick, 1960). But more surprisingly Axelrod and collaborators (Axelrod et al., 1961; Herting et al., 1961) showed that radiolabeled neurotransmitter monoamines were taken up into nerve terminals, which subsequently could be blocked by cocaine (now known as a triple monoamine reupake inhibitor) (Axelrod et al., 1961; Herting et al., 1961). Axelrod's work on the synthesis, metabolism, and reuptake of neurotransmitters provided lasting insights into the mechanisms of the chemical synapse. Today these insights form the basis for using MAO-enzyme-inhibitors and reuptake-inhibitors for the treatment of Parkinson's disease (MAO-B inhibitors) and major depression (e.g. MAO-A inhibitors and SSRIs), respectively (Stahl and Felker, 2008).

The development of SSRIs has dramatically changed the landscape of psychopharma-cotherapy of major depression. The Swedish pharmaceutical company Astra marketed the first SSRI zimelidine in 1982, but it was already withdrawn in 1983, because several patients developed the Guillain–Barré syndrome. Berend Olivier is co-developer of the first SSRI antidepressant in the world; named Fevarin (fluvoxamine) that is still used for major depression and obsessive–compulsive disorders. In 1984 it appeared first on the market in Switzerland followed by other European countries in 1985 and 1986. It was only in 1988 that Prozac (fluoxetine) appeared on the market in the USA as an antidepressant. Because of Eli Lilly's very effective marketing strategy, Prozac became the number one antidepressant. Many other SSRIs followed, such as paroxetine, sertraline, citalopram and escitalopram (the *S*-enantiomer of citalopram). SSRIs have replaced tricyclic antidepressants (TCAs) as the drugs of choice in the treatment of depressive disorders, not because of their better efficacy, but because of their improved tolerability and safety (Steffens et al., 1997). In 2006, however, a meta-analysis by the FDA showed an age-related side effect of SSRIs, indicating a higher risk for suicidal behavior among adults younger than 25 years (Henry and Demotes-Mainard, 2006). In retrospect, this may have been the case in one of the two shooters of the Columbine High School massacre, who was on fluvoxamine when he committed suicide after killing 13 people. Consequently, in the USA this drug rapidly lost favor and market share, and Solvay voluntarily withdrew fluvoxamine from the US market. Thereafter, many more casualties have been reported in the media in young people (some were victims of bullying) that used SSRIs, or just had started or had stopped SSRI treatment. This is very important because undertreated mood disorders can have severe negative consequences. Since 2004, after the FDA safety warnings and widespread media coverage, SSRI antidepressant use dramatically decreased, also in young people. Simultaneously, there was an increase in suicide attempts among young people (Lu et al., 2014). Thus, this FDA warning and media coverage might have produced unintended consequences. Recently, it was published that fluoxetine should remain the antidepressant of first choice in the treatment of young depressed patients, and appeared superior to paroxetine or a TCA (Qin et al., 2014). Thus, families and doctors should carefully weigh the risks and benefits, and closely follow and monitor to help control for the risks. Patients should never suddenly stop SSRI-medication, without consulting his/her general practitioner, because this may cause severe negative withdrawal side effects. Results of a comprehensive review of pediatric trials conducted between 1988 and 2006 suggested that the benefits of SSRI medications likely outweigh the increased suicide risk in children and adolescents with major depression and anxiety disorders (Bridge et al., 2007). Recently, it has been hypothesized that the use and withdrawal of SSRIs, MAO-inhibitors and TCAs are linked to REM sleep behavior disorder (Parish, 2007). This disorder is a clinical condition characterized by violent or frightening dreams which are “acted out” by the patient. Thus, more research is needed to understand why some young people due to SSRI medication become a risk for themselves (self-directed aggression) and/or their environment (externally-directed aggression) (Bouvy and Liem, 2012).

1.2. When is more better?

The most prescribed antidepressants are SSRIs, and are followed by serotonin–norepinephrine reuptake inhibitors (SNRIs). Although these compounds are effective in many patients suffering from severe major depression, a large number of patients fail to respond to drug therapy, often called treatment-resistant, probably depending on the type of their depression (Prins et al., 2011a).

Another group of patients encounter residual symptoms, such as impaired motivation and pleasure. Therefore, a role for dopamine in the treatment of depression has been postulated. Interestingly, when the dopaminergic system is co-targeted, antidepressant-treatment seems to be more effective (Prins et al., 2011a). These insights have led to the development of TRIs (Chepenik et al., 2009), which simultaneously block the 5-HT transporter (O'Connor et al., 2009), the norepinephrine

transporter (NET) and the dopamine transporter (DAT) (Prins et al., 2011a). It has been postulated that TRIs and DAT inhibitors are especially effective in treating anhedonia (i.e. loss of pleasure or pleasure deafness). Since cocaine is also a TRI there is increased awareness about abuse potential of TRI antidepressants (Fig. 1).

Previous studies by our group have shown that the TRI DOV 216,303 induced long-lasting enhancement of brain reward systems (Prins et al., 2012) and increased extracellular brain concentrations of monoamines (see also Fig. 6). The question remains what the contributions are of the separate monoamines in the treatment of anhedonia and more in general reward-related processes. Therefore, we will discuss the short-term and long-term effects of an SSRI (escitalopram), an SNRI (reboxetine), a DNRI (methylphenidate) and a TRI (DOV 216,303) on brain reward mechanisms as measured by intracranial self-stimulation (ICSS) (Fig. 1). Although, it has been shown that reboxetine is more effective in severely depressed patients, compared to fluoxetine (Montgomery, 1997; Massana, 1998), a meta-analysis study did not reveal superiority of reboxetine above TCAs or SSRIs in the treatment of major depression (Chuluunkhuu et al., 2008). The drugs only differed in the side effect profiles. Where fluoxetine-treated patients are more likely to experience nausea, hypersomnia and fatigue, reboxetine-treated patients experienced more constipation, painful urination (dysuria) and insomnia (Papakostas et al., 2008). Venlafaxine, milnacipran and duloxetine are dual-acting drugs, blocking both serotonin and noradrenaline transporters (SNRIs). Although some studies report differences in efficacy and onset of remission between SNRIs and SSRIs, however, this is quite rarely found (Clerc et al., 1994; Kasper et al., 1996). The main differences come again from side effects (Lopez-Ibor et al., 1996). In addition to the side effects due to blockade of the SERT (e.g., sexual dysfunction such as decreased ejaculation time, gain in body weight, suicidal thoughts or action in adolescents, etc.), the additional noradrenergic action sometimes causes anxiety and elevated blood pressure. Therefore, people who are susceptible to hypertension, heart disease or stroke have to be careful with taking SNRIs (Stahl et al., 2005) (Fig. 2).

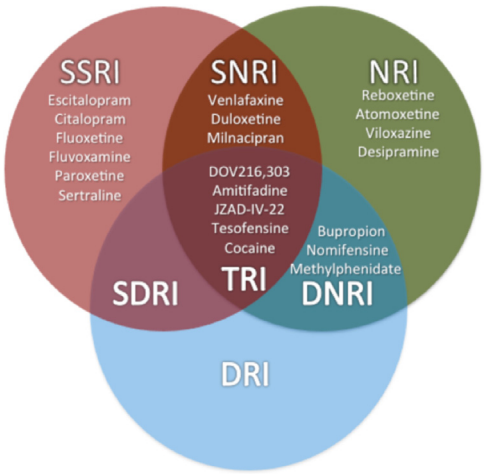

Fig. 1. Monoaminergic drugs blocking the serotonin, and/or norepinephrine and dopamine transporters. Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), dopamine reuptake inhibitor (DRI), and triple reuptake inhibitors (TRIs).

We will also discuss the effects of these drug treatments on the extracellular levels of the three monoamines in the synaptic cleft in the prefrontal cortex (PFC) and nucleus accumbens (NAc). Both brain areas play an important role in neurobiological mechanisms of depression and reward. These brain areas are part of two main dopaminergic tracts in the brain, the mesocortical and mesolimbic dopamine system, both originating in the ventral tegmental area (Nestler and Carlezon, 2006). Moreover, the NAc is an effective target for deep brain stimulation in treatment-resistant depression (Sturm et al., 2003). Furthermore, the PFC is innervated by serotonergic, norepinephrinergic and dopaminergic fibers from the raphe nuclei (dorsal raphe nucleus and median raphe nucleus), locus coeruleus (LC) and ventral tegmental area (VTA) respectively. This makes the PFC a very interesting brain area in the context of this review.

Finally, most drug trials ignore a possible division in subtypes of major depression. Therefore, it is discussed whether depressed patients with different symptoms, sometimes even opposite ones due to atypical or melancholic features, can be matched with the different drug treatments yet available.

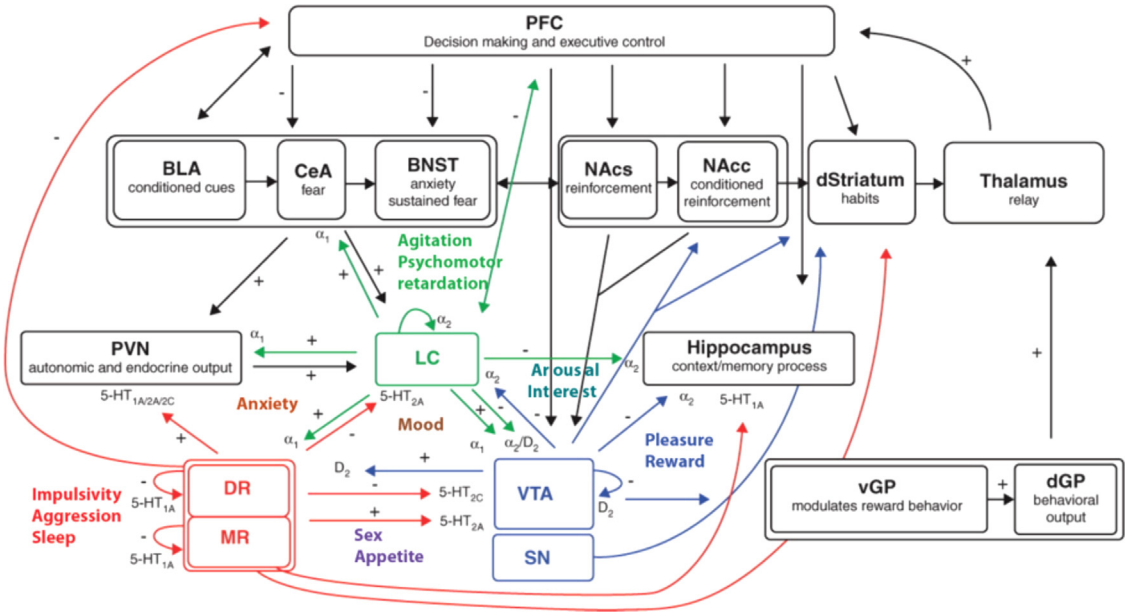

Fig. 2. Schematic overview of brain areas involved in major depressive disorder and their monoaminergic connections. In green are the noradrenergic projections. In red are the serotonergic projections. Finally, in blue are the dopaminergic projections. The figure is influenced and inspired by the many publications that support the finding of a high degree of connectivity between the different monoaminergic neurons: inspired by Koob and Volkow (2010). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. Specific monoamine transporter inhibitors, neurotransmitter content and reward mechanism

We have shown in rats treated with selective serotonin reuptake inhibitor (SSRI) escitalopram, norepinephrine reuptake inhibitor (NRI) reboxetine, dopamine–norepinephrine reuptake inhibitor (DNRI) methylphenidate, or the triple reuptake inhibitor (TRI) DOV 216,303, that these drugs differently affect neurotransmitter content in the prefrontal cortex (PFC) and the nucleus accumbens (NAc) by the use of the microdialysis technique (Prins et al., 2010, 2011a, 2011b, 2012).

2.1. SSRI, NRI or DNRI drugs differently affect monoamine levels in the prefrontal cortex (PFC)

2.1.1. Escitalopram and serotonin levels in the PFC

Acute administration of escitalopram led to an increase in extracellular 5-HT levels in the PFC, but no longer after chronic administration of the drug (Fig. 3). This was somewhat unexpected, because chronic treatment with SSRIs is generally supposed to increase 5-HT concentrations in the synaptic cleft (Fuller et al., 1994). These seemingly conflicting results may partly be explained by the fact that different SSRIs were used with a different biological half-life. As a consequence, some drugs are still on board, whereas others have left the body during the time of measurement. Traditionally, increased 5-HT concentrations in the synaptic cleft after chronic SSRI treatment are explained by the following assumptions: 1) serotonergic activity is controlled by somatodendritic 5-HT_{1A} autoreceptors in the raphe nuclei (RN), which upon binding by 5-HT inhibit the activity of 5-HT neurons as reflected by decreased serotonergic firing activity; 2) chronic SSRI treatment leads to an enhanced exposure of 5-HT to the somatodendritic 5-HT_{1A} autoreceptors in the RN; 3) due to this reduced number of somatic 5-HT_{1A} autoreceptors there will be less inhibition and thus chronic SERT blockade produces sustained increases in extracellular 5-HT levels (Bel and Artigas, 1993; Blier et al., 1987; Blier and de Montigny, 1990; Blier, 2010; Chaput et al., 1991; Haddjeri et al., 1998; Mongeau et al., 1994; Popa et al., 2010; Romero et al., 1996). It is generally accepted that chronic SSRI treatment decreases the number of somatodendritic 5-HT_{1A} autoreceptors in the RN, but our observation suggests that despite the reduced numbers of 5-HT_{1A} autoreceptors, the remaining ones are still functional. This is supported by a study in mice by Popa et al. (2010), showing that 5-HT levels were still increased in the RN following 28

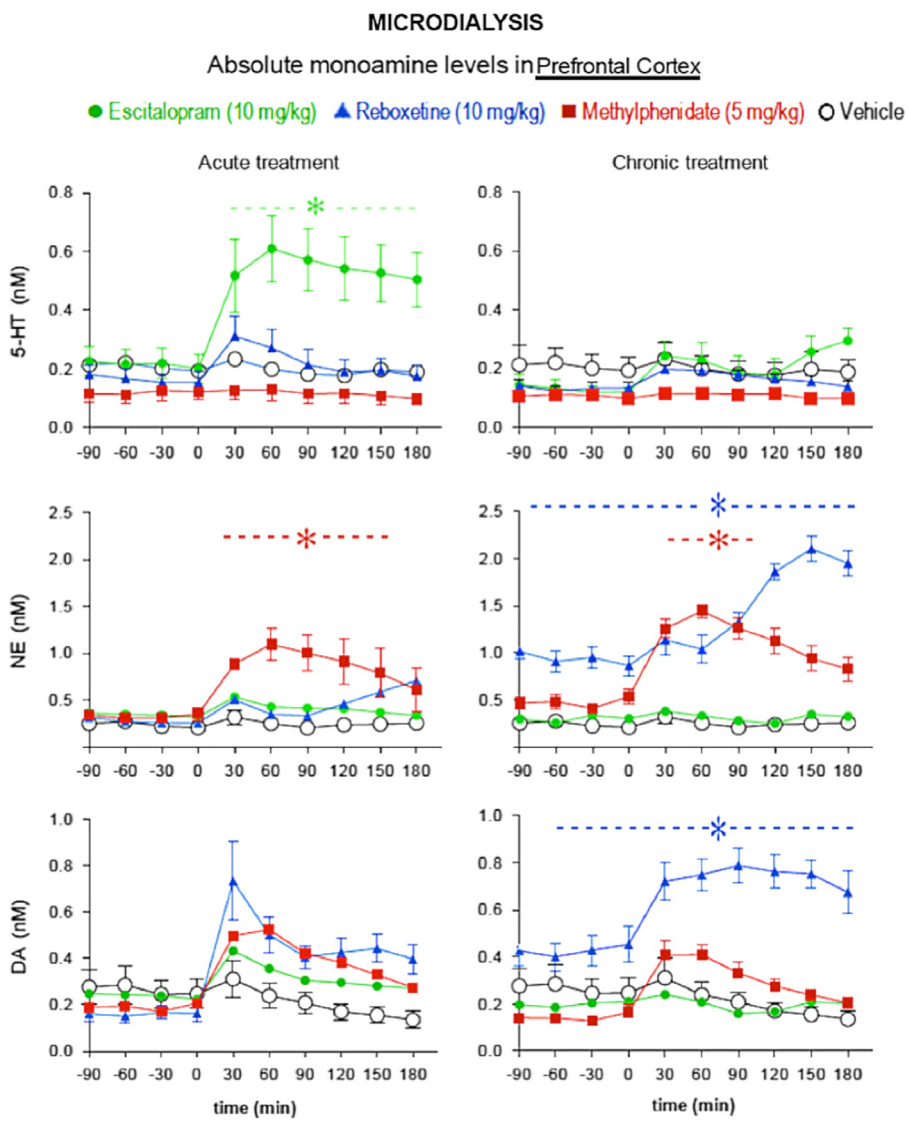

Fig. 3. Absolute monoamine concentrations in microdialysate from the prefrontal cortex (PFC) after a challenge (i.p.) with vehicle, escitalopram (10 mg/kg), reboxetine (10 mg/kg) or methylphenidate (5 mg/kg) (left panels) or chronically drug-treated animals (right panels). Time points −90 till 0 min represent baseline measurements. At $t=0$ min a single injection was given. And six 30-min samples were taken up to 3 h after the challenge. $^{*}P<0.05$ compared to vehicle with Dunnett's test.

days of the SSRI fluoxetine treatment; however, extracellular 5-HT levels in the hippocampus were no longer increased. Thus, whether real 5-HT differences can be observed also depends on the localization where microdialysis is performed, presynaptically or postsynaptically. In addition, the 5-HT_{1A} receptor agonist 8-OH-DPAT gave a similar decreased 5-HT response in vehicle and chronic citalopram treated animals, suggesting that there are still sufficient 5-HT_{1A} autoreceptors present in the RN involved in feedback (Nestler and Carlezon, 2006). Moreover, autoreceptors still respond to a 5-$HT_{1A/1B}$ receptor antagonist after chronic citalopram treatment by increasing 5-HT in the frontal cortex and dorsal hippocampus (Ceglia et al., 2004). Previously, it has clearly been shown via neurophysiological techniques that chronic SSRI treatment reduces the number of 5-HT_{1A} autoreceptors (Blier et al., 1987; Blier and de Montigny, 1990; Blier, 1991; Chaput et al., 1991; de Montigny et al., 1990), but the remaining (decreased number of) 5-HT_{1A} autoreceptors are still functional as shown by microdialysis (Gundlah et al., 1997). Recently, the FDA approved vilazodone and vortioxetine for the treatment of major depression. These newer compounds are both SSRIs, but at the same time also act as 5-HT_{1A} receptor agonists. Thus, indeed suggesting that 5-HT_{1A} autoreceptors still can be active after chronic SSRI treatment. These new drugs seem to have less sexual side effects than the normal SSRIs without additional 5-HT_{1A} binding affinities (Bijlsma et al., 2014; Snoeren et al., 2014).

2.1.2. Reboxetine and norepinephrine levels in the PFC

As expected, both the acute and chronic treatment with NRI reboxetine increased norepinephrine concentrations in the PFC (Fig. 3). Remarkably, chronic reboxetine treatment also increased baseline dopamine levels in the PFC. This finding is in agreement with studies in which desipramine and reboxetine increased basal levels of dopamine and norepinephrine in the PFC. Although DATs are almost absent in the PFC, the fact that dopamine is taken up via NET can explain the observed increased dopamine levels after NET-blockade by reboxetine. Chronic treatment with reboxetine led also to increased baseline concentrations of dopamine and norepinephrine in the PFC, which might be explained by desensitization of terminal α_2-adrenoceptors, which normally inhibit norepinephrine release.

2.1.3. Methylphenidate and dopamine levels in the PFC

Surprisingly, both acute and chronic treatment with the DNRI methylphenidate (in a dose of 5 mg/kg) did not significantly increase dopamine concentrations in the PFC, although there was a tendency. As expected chronic methylphenidate also increased norepinephrine concentrations in the PFC, because methylphenidate also blocks the NET (see Fig. 3).

2.2. SSRI, NRI or DNRI drugs differently affect monoamine levels in the nucleus accumbens (NAc)

As expected, both acute and chronic methylphenidate treatment significantly increased extracellular dopamine concentrations in the NAc. The other used reuptake inhibitors affected neither 5-HT nor dopamine in the NAc (Fig. 4). Recently, it was shown that bupropion and nomifensine, both DNRIs, could alleviate therapeutically depressive symptoms associated with Parkinson's disease in primates and humans (Hansard et al., 2002; Raskin and Durst, 2010). Bupropion, however, may have amphetamine-like abuse potential as observed in preclinical studies, in which animals substituted bupropion for amphetamine in a drug-discrimination task (Bevins et al., 2006). The abuse potential of bupropion is apparent from following findings: bupropion is self-

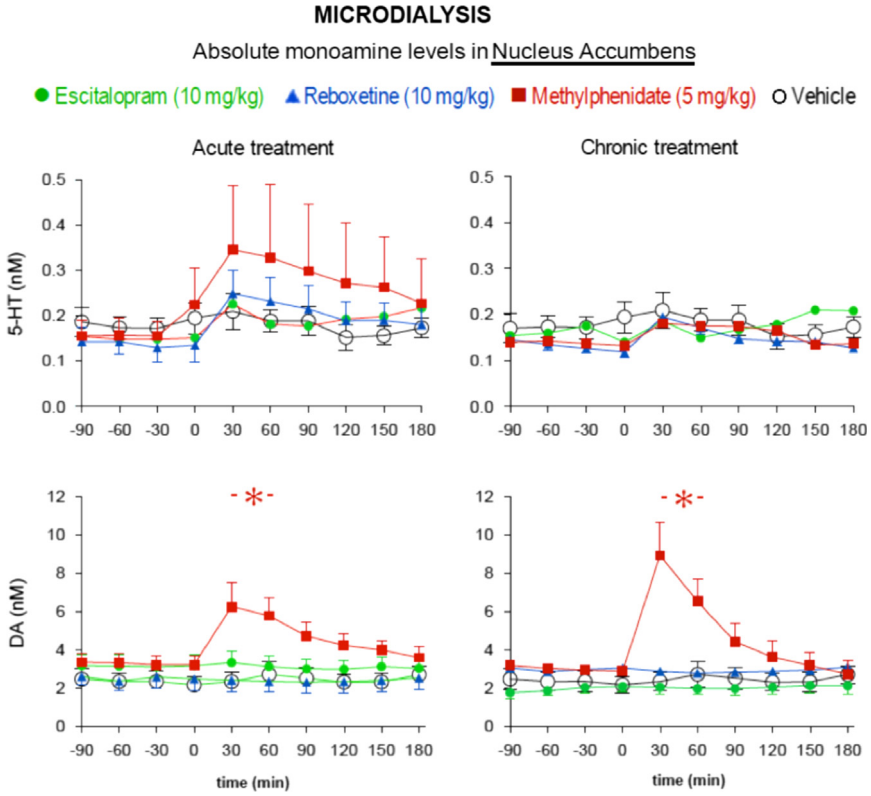

Fig. 4. Absolute monoamine concentrations in microdialysate from the nucleus accumbens (NAc) after a challenge (i.p.) with vehicle, escitalopram (10 mg/kg), reboxetine (10 mg/kg) or methylphenidate (5 mg/kg) (left panels) or chronically drug-treated animals (right panels). Time points −90 till 0 min represent baseline measurements. At $t=0$ min a single injection was given. And six 30-min samples were taken up to 3 h after the challenge. Norepinephrine levels were below detection limit. $^{*}P<0.05$ compared to vehicle with Dunnett's test.

administered intravenously by monkeys (Bergman et al., 1989) and rats (Nicholson et al., 2009) and in humans, bupropion increases arousal, mood and euphoria (Cousins et al., 2001). Methylphenidate is also known for its abuse potential (Kollins, 2003). Nevertheless, this has never been a reason to retract it from the market.

2.3. SSRI, NRI or DNRI and reward mechanisms

None of the treatments changed the baseline ICSS thresholds (Fig. 5). Methylphenidate-challenges at days 1 and 8 of the chronic treatment showed tendencies to decrease intracranial self-stimulation (ICSS) thresholds (Engblom et al., 2001), only a methylphenidate-challenge at day 14 of the chronic treatment resulted in a significant enhancement of brain reward systems as reflected by decreased ICSS thresholds (see Fig. 5). Increased extracellular levels of dopamine in the NAc (see Fig. 4) paralleled the observed rewarding effects of methylphenidate (see Fig. 5). This is in accordance with the known action of methylphenidate that, like other psychostimulants, immediately increases mesolimbic dopamine concentration in humans (Volkow et al., 2001). The rewarding effects, measured by the facilitation of ICSS behavior, might be an explanation why this drug is gaining popularity in humans for its hedonic properties (Teter et al., 2006). In agreement, rewarding and reinforcing properties of methylphenidate have been shown in Wistar rats, during both conditioned place preference (Fuller et al., 1994) and self-administration (Aghajanian et al., 1990).

Chronic treatment with the SSRI escitalopram did not alter ICSS thresholds, but remarkably, acute administration of escitalopram increased ICSS thresholds. The SSRI fluoxetine was previously used in ICSS experiments. To our knowledge, this is the first study in which the effects of escitalopram on ICSS behavior are investigated. The present results are in agreement with these earlier findings, in which the rate of responding for reward was decreased by acute administration of fluoxetine in rats (Blier et al., 1987), suggesting an inhibitory influence of 5-HT on reward systems. However, other scientists (Lee and Kornetsky, 1998) showed that acute as well as chronic administration of fluoxetine increased ICSS thresholds, while in our study chronic treatment with escitalopram failed to alter ICSS thresholds. We can only speculate about the reason for these differences between the two SSRIs. For instance, fluoxetine and escitalopram differ in spontaneous activity of dopaminergic neurons in the VTA (Prisco and Esposito, 1995).

Unexpectedly, administration of the NRI Reboxetine did not have an impact on ICSS, while nomifensine, a NET-blocker, facilitates ICSS behavior and enhances motivation for ICSS (Schaefer and Michael, 1992). The antidepressant desipramine also possesses NET blocking capacity and lowers ICSS thresholds 30 min after treatment (Paterson et al., 2008). These discrepancies might be explained by differences in transporter binding profiles and in ICSS protocols. The interpretation of older ICSS studies is hampered by the fact that rate-dependent measures of self-stimulation were used, which makes it difficult to differentiate between drug-induced changes resulting from reward alterations or motor performances. In our study, no differences in response latencies were found, indicating that motor dysfunctions could not be an explanation for the observed effects on ICSS thresholds. Finally, reboxetine did not result in alterations of brain reward circuitry, at doses that normally induce behavioral changes.

2.4. Triple reuptake inhibitor (TRI) DOV 216,303 treatment affects monoamine levels in the PFC

As expected, the TRI DOV 216,303 (in a dose of 20 mg/kg p.o.) significantly increased 5-HT, norepinephrine and dopamine concentrations, both after acute and chronic treatment in the PFC (Fig. 6). Baseline monoamine concentrations, however, were not altered. The DOV 216,303 effects are more robust than the data of

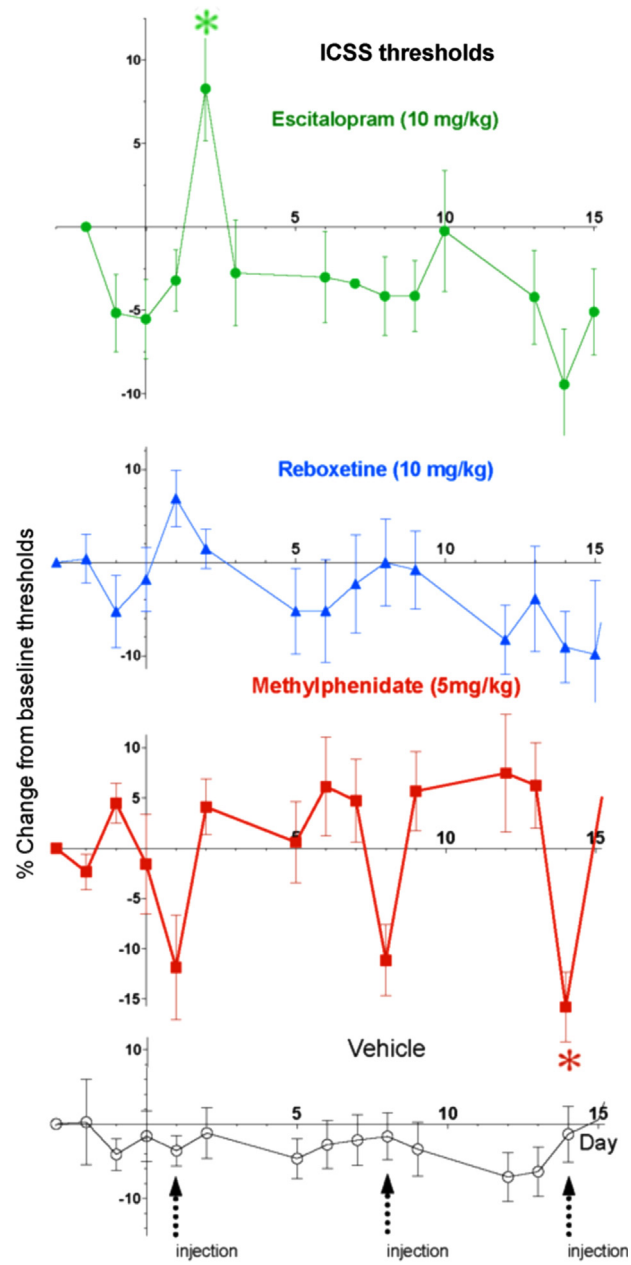

Fig. 5. Percentage changes in ICSS thresholds (±S.E.M.) after drug treatment. Animals were treated with either vehicle, methylphenidate (5 mg/kg), reboxetine (10 mg/kg) or escitalopram (10 mg/kg) for 14 days and ICSS tests were performed before drug treatment, except for days 1, 8 and 14, when animals received drug treatment 1 h before ICSS testing. $^{*}P<0.05$ compared to vehicle with Dunnett's test.

SSRI, NRI or DNRI drugs, possibly due to the fact that DOV 216,303 blocks all three monoamine transporters SERT, NET and DAT. Unfortunately, we do not have the effects of DOV 216,303 on dopamine in the NAc of rats, but previously we have shown that DOV 216,303 increases dopamine in the NAc of mice (Heesch et al., unpublished findings).

2.5. TRI and reward mechanisms

Previously, we have shown that the injection of DOV 216,303 (in a dose of 20 mg/kg, p.o.) (see Fig. 7) decreased ICSS thresholds in rats; surprisingly this effect was relatively long-lasting (Prins et al., 2012). ICSS thresholds are considered as a direct measure of brain reward function in rats and mice (Markou and Koob, 1992;

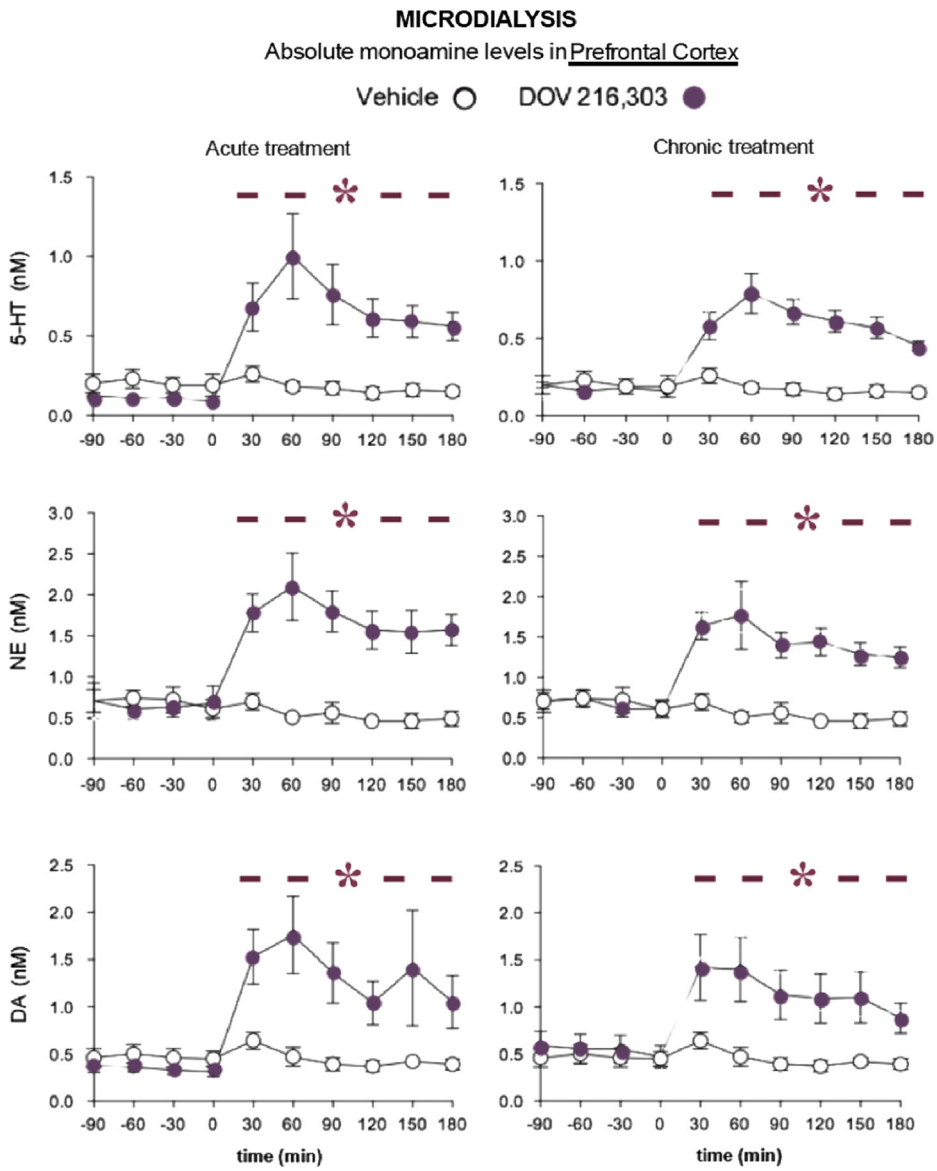

Fig. 6. Absolute monoamine concentrations in microdialysate from the prefrontal cortex (PFC) after a challenge (i.p.) with vehicle or DOV 216,303 (20 mg/kg, p.o.) (left panels) or chronically drug-treated animals (right panels). Time points −90 till 0 min represent baseline measurements. At $t=0$ min a single injection was given. And six 30-min samples were taken up to 3 h after the challenge. $^{*}P<0.05$ compared to vehicle with Dunnett's test.

Carlezon and Chartoff, 2007; Kenny, 2007). Drug-induced lowering of ICSS thresholds can be explained by increased reward signaling resulting in potentiating the reward perceived by ICSS thresholds (Kenny, 2007). The relatively long lasting stimulatory effects (up to 6 h) on brain reward by DOV 216,303 observed in the current study are quite different from the transient effects of psychostimulant drugs like amphetamine (Leith and Barrett, 1976; Lin et al., 1999) and cocaine (Kenny et al., 2003), which only decrease ICSS thresholds for a relatively short period (from 15 min up to 3 h). The DNRI bupropion dose-dependently enhanced brain reward function 30 min after treatment, in a similar way as methylphenidate (see Fig. 5). But this effect was relatively short lasting, because 24 h after treatment ICSS thresholds were back to baseline levels (Cryan et al., 2003). Furthermore, the NRI desipramine lowered ICSS thresholds 30 min after administration, but had no effect after chronic treatment (Paterson et al., 2008). Although chronic fluoxetine did not have an effect itself on brain reward systems, it did alter the ability of amphetamine to potentiate ICSS reward (Lin et al., 1999). However, other studies showed opposite

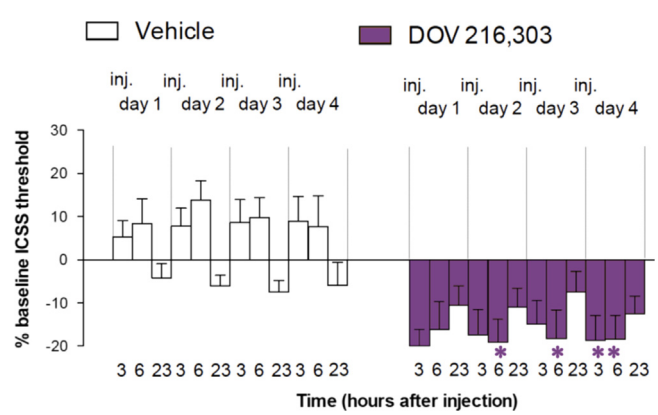

Fig. 7. Percentage changes in ICSS thresholds (±S.E.M.) after drug treatment. Animals were treated with either vehicle or DOV 216,303 (20 mg/kg, p.o.) for 4 consecutive days and ICSS tests were performed before drug treatment, when animals received drug treatment 1 h before ICSS testing. $^{*}P<0.05$ compared to vehicle with post-hoc t-test.

effects: acute as well as chronic treatment with fluoxetine elevated reward thresholds (Lee and Kornetsky, 1998). Moreover, another study showed that chronic blockade of the serotonin transporter by fluoxetine, or a deletion of this transporter in SERT knockout rats, results in reduced responding for natural food reward (Sanders et al., 2007), suggesting that the serotonin system is involved in reward-related processes (Kranz et al., 2010). So, our data showed an increased sensitivity of brain reward systems by DOV 216,303 for a longer period than reported in these other studies. The combination of increasing all three monoamines at the same time might be a possible explanation for this enhancement of brain reward function, which might be a key therapeutic advantage in the treatment of anhedonia.

Since DOV 216,303 enhances dopaminergic neurotransmission, its possible use as an antidepressant drug raises concerns related to its abuse potential. Cocaine (which is like DOV 216,303 also a TRI) also increases dopamine neurotransmission, and is known for its intrinsic abuse potential and reinforcing effects (Kuhar et al., 1991). It is known that rats titrate their patterns of self-administration of intravenous cocaine (Kenny et al., 2003), heroin (Kenny et al., 2006) or nicotine (Kenny et al., 2006) at a level that achieves maximal drug-induced lowering of ICSS thresholds. Thus, the stimulatory effects of these drugs on brain reward systems represent an important source of positive reinforcement that motivates habitual consumption (Kenny, 2007). Recently, experiments assessing the potential abuse liability of DOV 216,303 showed that the compound only partially substituted cocaine in a drug-discrimination assay in rats and produced locomotor sensitization in mice at doses that are at least six times higher than the minimally effective dose in antidepressant tests (Caldarone et al., 2010). Furthermore, a clinical trial did not mention adverse effects as abuse potential of DOV 216,303 (Beer et al., 2004; Skolnick et al., 2006). Moreover, a recent study showed that amitifadine (DOV 21,947 or EB-1010, the active enantiomer of DOV 216,303) significantly improved symptoms (including anhedonia) in patients with major depressive disorder without observing adverse side effects (Tran et al., 2012). Nevertheless, more experiments have to be performed before it can be concluded that DOV 216,303 has no addictive properties at all. In conclusion, the TRI DOV 216,303, which has previously shown to have an antidepressant-like action (Breuer et al., 2008; Caldarone et al., 2010), can activate brain reward systems for a relatively long period (see Fig. 7). Recently, it was shown that the TRI tesofensine in humans did not have drug abuse potential 48 h after drug administration and the effects of tesofensine (a cocaine-like structure) were either lower than or not different from those of bupropion (Schoedel et al., 2010), while JZAD-IV-22, also a TRI, does seem to have less abuse potential (Caldarone et al., 2010). These findings may be explained by a very slow onset of action. After taking it orally, it takes approximately 6 h for blood levels to peak and persists in the body for weeks (half-life of approximately 220 h). With the TRI cocaine, peak blood levels and peak brain (striatum) levels are achieved in minutes and the half-life is less than 1 h (Volkow et al., 1997). Therefore, it is hypothesized that TRIs that produce a relatively slow increase in brain DA levels, have less or no abuse potential, nevertheless can still be used to treat anhedonia in the longterm.

3. Discussion

3.1. Different endophenotypes of major depression

The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5, latest version) (Association of American Psychiatry, 2013) describes major depressive disorder in adults as a condition in which an individual experiences at least 2-week of depressed mood (i.e. sad, empty or hopeless) and/or loss of interest and pleasure (anhedonia) accompanied by at least four additional symptoms of depression nearly every day and most of the day. The latter includes significant changes in appetite or weight gain or weight loss (> 5% change over 1 month). Other additional symptoms are insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, impaired concentration or indecisiveness, and recurrent thoughts of death or suicidal ideation or any attempt. It is important that the symptoms are not attributable to a substance or medical condition and they should cause significant distress or impairment. In the DSM-5 different specifiers are given to diagnose the specific different subcategories of major depression, including “with melancholic features”, “with atypical features”, “with anxious distress”, “with mixed features”, “with mood-congruent psychotic features”, “with mood-incongruent psychotic features”, “with catatonia”, “with peripartum onset”, and “with seasonal pattern”. Furthermore, specifiers are given for severity and chronicity. For exact wording and more details, please check the DSM-5 manual (Association of American Psychiatry, 2013).

Remarkably, some symptoms in the DSM-5 description of major depression are extreme opposites of each other and lead to different subcategories of major depression (Horwath et al., 1992; Gold and Chrousos, 2002; Lamers et al., 2010). These opposite symptoms strongly suggest differences in underlying neuropsychopathology. Here, we will especially focus on major depression with melancholic features and major depression with atypical features (see Table 1). Unfortunately, most drug studies ignore the presence of subcategories in major depression.

Melancholic patients experience loss of appetite and accompanied weight loss, insomnia and psychomotor agitation, while in contrast atypical depression is associated with increased appetite, weight gain, fatigue, hypersomnia and psychomotor retardation (Levitan et al., 1997; Baldwin and Papakostas, 2006). Melancholic depression is furthermore associated with increased generalized anxiety, less responsiveness to environmental cues, a decreased sympathetic activity, and both a hyperactive corticotropin-releasing factor (CRF) system and hypothalamus-pituitary-adrenal (HPA) axis and, consequently leading to an inhibition of growth and reproduction cycles and altered immune function, leading to enhanced infection susceptibility (Gold and Chrousos, 1999; Elenkov and Chrousos, 1999; Wong et al., 2000b; Stewart et al., 2005). Recently, it became clear that acute stress is immune enhancing, because it enhances dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function. In contrast, chronic stress suppresses immune function, making the organisms more vulnerable for infection (Dhabhar et al., 2012).

Atypical depression, on the other hand, is associated with lethargy, increased reactivity to environmental cues (i.e., depressed mood can lift during the depressive phase, although only temporarily), CRF deficiency, down-regulation of the HPA axis, and an altered immune function, making someone more vulnerable for inflammation (Horwath et al., 1992; Levitan et al., 1997; Lamers et al., 2010). The DSM-5 defines major depression with atypical features by i) mood reactivity (i.e., mood brightens in response to actual or potential positive events, i.e., paradoxical anhedonia) and ii) at least two of the following: significant weight gain or increase in appetite; hypersomnia (sleeping too much); heavy, leaden feelings in arms or legs; and long-standing pattern of interpersonal rejection sensitivity that results in significant social or occupational impairment. In addition, it has been shown that patients with atypical depression often suffer from co-morbid social phobia. Most depressed patients experience mixed symptoms from either subtype. These patients are mostly diagnosed with moderate depression (Levitan et al., 1997) and do often not respond adequately to antidepressants (Fries et al., 2009; Fournier et al., 2010). Patients with pure melancholic (25–30%) or pure atypical features (15–30%) generally have a more severe course of disease, and antidepressant treatment is most effective in these most severely depressed patients (Levitan et al., 1997; Fournier et al., 2010).

Table 1
Major depressive disorder categorized on melancholic and atypical features based on the DSM-5, neurobiology, neuroendocrinology and immunology. Check DSM-5 for exact wording (Association of American Psychiatry, 2013).

Major depressive disorder	
Atypical features	Melancholic features
Paradoxical anhedonia (short term pleasure)	Anhedonia (no pleasure in most activities)
Mood brightens in reactivity to pleasurable stimuli	A failure of reactivity to pleasurable stimuli
Weight gain or increased appetite (comfort eating)	Weight loss or decreased appetite
Excessive sleep or sleepiness (hypersomnia)	Early morning awakening (hyposomnia)
Fatigue and energy loss	Marked psychomotor retardation or agitation
Heavy feelings in arms and legs (leaden paralysis)	
Apathy (and/or lethargy)	Hyperarousal (and/or anxious behavior)
Interpersonal rejection hypersensitivity that results in significant social impairment	Excessive or inappropriate guilt
Social phobia	Generalized anxiety
Underlying neurobiology and neuroendocrinology	
Hypoactive LC noradrenergic system	Hyperactive LC noradrenergic system
Central CRF deficiency	Activated central CRF system
Hypoactive HPA-axis	Hyperactive HPA-axis
High feedback suppression by cortisol	Low feedback suppression by cortisol
Immunology	
Increased inflammatory response and/or sickness behavior (more plasma IL-6, TNF-α, CRP)	Increased vulnerability to infections
Physiology	
Increased sympathetic activity: increased systolic BP; metabolic syndrome: more triglycerides, increased BMI, decreased HDL cholesterol levels	Decreased sympathetic activity Glucocorticoid resistance

3.2. *Different brain mechanisms involved in atypical and melancholic features of depression*

Patients are often characterized and diagnosed for depression based on a mixture of symptoms listed in the DSM-5 (Association of American Psychiatry, 2013). Irrespective of the more melancholic or atypical features of depression, first-line SSRI antidepressant treatment is mostly used for all patients. It is not very logic to assume that depressions with opposite symptoms (see Table 1) have the same underlying disturbances in brain functioning and will equally benefit from similar drug treatment. Fig. 2 represents a schematic representation of different brain areas and their connections involved in major depression (Prins et al., 2012). The different roles of monoamines in different subsets of symptoms have been extensively discussed and reviewed, but most studies do not distinguish between the opposite symptoms of depression (e.g., no difference is made between insomnia and hypersomnia; less eating and more appetite; depressed mood and mood reactivity) as can be observed in melancholic and atypical depression, respectively.

In the following sections, specific symptoms are linked to particular brain abnormalities. However, it should be noted that it is not easy to link one particular symptom to a specific disturbance in one specific brain area, as most brain areas participate in more complex interacting brain networks, as shown in Fig. 2 (Fuster, 2001). Below are the symptoms shown of atypical and melancholic depression and the associated specific brain abnormalities, often derived from preclinical studies.

3.2.1. *Mood reactivity or anhedonia*

One key regulatory pathway for motivation and experience of pleasure and reward is the dopaminergic mesolimbic pathway arising in the VTA and projecting to the nucleus accumbens (NAc), bed nucleus of stria terminalis (BNST), amygdala and septum (Dunlop and Nemeroff, 2007). Hedonic hotspots furthermore include the shell of the NAc and ventral pallidum (Berridge and Kringelbach, 2008). During stress, glucocorticoids may facilitate dopaminergic transmission especially in the NAc-shell, but not in the NAc-core (Marinelli and Piazza, 2002). So in a hypoactive stress system, as present in atypical depression (Table 1), lower glucocorticoid levels are present and dopaminergic transmission in the NAc may be decreased, leading to deficiencies in experiencing pleasure. On the other hand, in the melancholic subtype, a chronic activated CRF system and a subsequent increased dopaminergic system might lead to desensitization of the reward system, leading to anhedonia as well, but via different mechanisms (Table 1) (Leshner and Koob, 1999; Dunlop and Nemeroff, 2007). Remarkably, it has been shown that glucocorticoids also affect the efficacy of the enzyme tryptophan-hydroxylase, thereby stimulating the synthesis of 5-HT (Azmitia and McEwen, 1969; Korte-Bouws et al., 1996). In addition, there is substantial evidence that increased hippocampal 5-HT levels are associated with an increased anxiety state (van der Staay et al., 2009).

3.2.2. *Increased or decreased appetite*

In depression with atypical features more often increased appetite is observed as compared to melancholic depression, whereas melancholic depression is characterized by a much higher HPA axis activation (Penninx et al., 2013). It looks straightforward: more eating, more obesity. But like often, it is much more complex! A typical example of chronic activation of the HPA axis is Cushing's syndrome (often caused by adrenal tumor cortisol hyperproduction). These patients often have melancholic depression (and/or psychotic features), generalized anxiety, obesity, diabetes mellitus, and hypertension (Hotamisligil, 2006; Tirabassi et al., 2014). It is well known that chronic elevations of glucocorticoids produce the metabolic syndrome: insulin resistance; glucose intolerance; skeletal muscle wasting; dyslipidemia; and central adiposity (van Raalte et al., 2009). Recently it was shown that depressed people with atypical features, paradoxically more often suffer from the metabolic syndrome than melancholic depressed people (Lamers et al., 2010; Seppala et al., 2012). Several explanations can be given for this seemingly contradictory observation. In depressed people, changes in eating patterns might also be a result of a disturbance in reward perceived from food, regulated by the mesolimbic reward centers. First of all, people with atypical depression still respond to positive events. By eating palatable food (high in sugar and fat) these patients trigger neuroadaptive responses (via dopamine D2 receptors) in brain reward circuitries (including NAc) similar to drugs of abuse (Saper et al., 2002; Zheng and Berthoud, 2007; Johnson and Kenny,

2010; Kenny, 2011). In agreement, it was previously shown that severely depressed patients experience greater reward after amphetamine intake and had altered brain activation of the ventrolateral PFC, orbitofrontal cortex, caudate and putamen, compared with mild depressed patients and healthy controls (Tremblay et al., 2002). In the short term, above described behavioral adaptive response can be seen as self-medication (i.e. comfort eating), but in the long-term compulsive eating produces obesity and metabolic syndrome. This new allostatic state is a risk for entering a downward spiral, because obesity produces a general health risk: lipid accumulation causes adipocytes to directly secrete IL-6, TNF-α and the monocyte chemoattractant protein 1 (MCP-1), which result in a chronic inflammatory state. This inflammatory state negatively affects diabetes mellitus, cardiovascular disease, depression and even cancer (Capuron and Miller, 2011). Recently, it was shown that patients with treatment-resistant depression could successfully be treated with infliximab, a TNF-α antibody, if these patients had transcriptional signatures related to glucose and lipid metabolism (Mehta et al., 2013). Thus, an inflammatory state due to obesity might further worsen both depression and general health condition.

Besides the mesolimbic dopaminergic reward pathway, other key players are the noradrenergic and serotonergic pathways innervating the ventromedial nucleus of the hypothalamus (VMH), involved in the regulation of interest and "drive". Therefore, this area is thought to be important to regulate appetite drives and vegetative functions, including sexual functioning (Adamec, 1976; Gold and Chrousos, 2002; Dunlop and Nemeroff, 2007) (see also review of Dr. Jan Veening in present EJP issue (Veening et al., 2014)). Furthermore, disturbances in the VMH may underlie less appetite and weight loss, in particular in melancholic depression. Anorexia-like symptoms, weight loss, early satiety, fatigue, muscle wasting, and depression can be observed in nearly half of cancer patients (i.e. cachexia). This disease state is produced by the very high levels of Il-1, IL-6, and IFN-γ (Esper and Heidrich, 2005; Andreasson et al., 2007; Shelton and Miller, 2010). Thus, a neuroimmune-link is present in cancer-related depression associated with weight loss.

3.2.3. Fatigue or agitation

Fatigue and energy loss are primarily linked to the atypical subtype of depression, while the complete opposite symptoms psychomotor redardation and/or agitation belong to atypical depression (Lamers et al., 2010). Fatigue can be divided into physical or mental fatigue, which both may have different neurobiological pathways involved. Mental fatigue might be related to cognitive dysfunction and lack of motivation. These symptoms might be linked to cortical brain areas. Physical fatigue, associated with leaden paralysis, tiredness and exhaustion of the body, is partly driven by a dysfunctional dopaminergic signaling in the striatum (Flint et al., 1993) and other motor controlling brain areas such as the cerebellum. The later is innervated by noradrenergic fibers (Stahl et al., 2003). It also has been suggested that too low norepinephrine and dopamine concentrations in the PFC are responsible for fatigue symptoms (Arnsten, 2009). Recently, it has been suggested that increased activity of the immune system (e.g. increased pro-inflammatory cytokine levels in autoimmunity, obesity or psychological stress) produces symptoms of both mental and physical fatigue by reducing availability of the co-factor tetrahydrobiopterin (BH4), which stimulates the enzyme phenylalanine hydroxylase, which converses L-phenylalanine to L-tyrosine (precursor of dopamine) (Felger et al., 2013). Thus, increased inflammation may lower dopamine concentrations in the basal ganglia and consequently produce fatigue (Miller et al., 2014).

Studies in depressed patients with psychomotor retardation showed lower concentrations of the metabolite of dopamine, homovanillic acid in cerebrospinal fluid (Praag et al., 1975; Banki, 1977). In these patients the motor controlling brain areas, such as dopaminergic mesocortical and nigrostriatal pathways, are hypoactive and may underlie these symptoms (Stein, 2008). Symptoms of retardation of motor functions are probably regulated by dysfunctional striatal dopaminergic transmission, as patients with Parkinson's disease experience similar symptoms as depressed patients (Flint et al., 1993). On the other hand, hyperactivity of the HPA axis might be associated with agitation, linking it to melancholic depression (Carroll et al., 1981; Mitchell et al., 1996). In addition, it has been shown that dopaminergic functioning in the left caudate, bilateral putamen and NAc, left parahippocampus and dorsal brainstem is lower in depressed patients with psychomotor retardation (Martinot et al., 2001).

3.2.4. Apathy or hyperarousal

Changes in apathy and hyperarousal, as part of major depression, have been associated with dysfunctional neuronal activation of the medial prefrontal cortex (mPFC), including the anterior cingulate and orbitofrontal cortex (Mayberg et al., 1999; Price and Lucki, 2001; Davidson et al., 2002). The PFC is involved in overall cognitive functioning that allows an organism to get things done; problem solving and time planning, reinforcement, reappraisal and suppression of negative affect (Koenigs and Grafman, 2009; Koob and Volkow, 2010). The frontal cortex is highly innervated by inhibitory serotonergic fibers from the midbrain raphe nucleus (RN) (Sastry and Phillis, 1977; Molliver, 1987) with the dorsal raphe nucleus projecting to the PFC and striatum and the median raphe nucleus innervating hippocampus and striatum. It has been suggested that in particular the dorsal raphe nucleus is involved in affective disorders, because psychostimulants activate the dorsal raphe nucleus, but not the median raphe nucleus (Molliver, 1987). Moreover, the cingulate cortex and PFC are inhibited by noradrenergic fibers from the locus coeruleus (LC) (Dillier et al., 1978; Gold and Chrousos, 2002; Berridge and Waterhouse, 2003). During stress, the HPA axis becomes activated and subsequently activates the LC-noradrenergic systems, which in turn further inhibit the PFC, thereby favoring more rapid and basal responses over more complex responses (Arnsten, 2000).

Melancholic depression is characterized by a prolonged and intensified stress system. A hyperactive noradrenergic system in the LC innervates and activates the CRF-system in the amygdala (Korte, 2001; Wong et al., 2000b). Other NE projections from the LC to the PFC are strengthened and consequently the PFC is more inhibited (see Table 1). Due to this lower PFC activity, the amygdala is less inhibited and consequently more anxiety can be expected due to higher amygdala activity (Arnsten, 2009). Furthermore, due to increased HPA axis activity in melancholic depression, glucocorticoids will stimulate the central amygdala and bed nucleus of the stria terminalis (BNST), thereby further increasing anxiety levels (for reviews see Schulkin et al. (1998), Korte (2001), and Korte et al. (2005)). In contrast, it is well known that chronic HPA axis activation may result in a less well functioning hippocampus due to inhibition of neurogenesis in the dentate gyrus (DG) and dendritic shrinkage in CA3 of the hippocampus (McEwen and Seeman, 1999; McKittrick et al., 2000; Miller et al., 2003, 2012; Nacher and McEwen, 2006; Nacher et al., 2007; Radley et al., 2005). This finally will result in impaired contextual processing and pattern separation, which will contribute to an allostatic state of generalized anxiety (Kheirbek et al., 2012).

Atypical depression is characterized by a hypoactive norepinephrinergic and HPA-CRF system and the PFC receives less inhibitory innervation by the LC, this will result in a hyperactive PFC (Gold and Chrousos, 2002). Furthermore, the PFC receives dopaminergic projections from the VTA (Williams and Goldman-Rakic, 1998). This might result in a state of apathy.

3.2.5. Hypersomnia or insomnia

The neurophysiology of sleep and how it is changed in major depression is very complex (Mignot, 2001; Wisor et al., 2001; Zheng and Berthoud, 2007); it is, therefore, beyond the scope of this review to extensively discuss the neurobiology of sleep disturbances in the different subtypes of major depression. In general, states of arousal are regulated by the hypothalamic sleep–wake switch, which consists of sleep-promoting neurons in the ventrolateral preoptic area and wake-promoting neurons in the tuberomammillary nucleus (Saper et al., 2001). Noradrenergic and serotonergic projections from the LC and dorsal and median RN, respectively, run through the hypothalamus, where they are combined with histaminergic projections from the tuberomammillary nucleus. Orexin/hypocretin (Peyron et al., 1998) and melanin-concentrating hormone (Bittencourt et al., 1992) also join this projection. Histaminergic projections from the tuberomammillary nucleus must be activated for normal wakefulness to occur (Strecker et al., 2002). Disturbances in these projections might lead to an altered sleep–wake cycle, which will result in insomnia in melancholic depression and excessive sleep and hypersomnia in atypical depression (Gold and Chrousos, 2002; Lamers et al., 2010). Melancholic depression is characterized by a general HPA axis overactivity; therefore it is speculated that this may produce early morning awakening (insomnia), although other explanations cannot be excluded (for review see Fries et al. (2009)).

Atypical depression is also characterized by hypersomnia, which may be treated with modafinil (Dunlop et al., 2007). Modafinil is a wake-promoting agent and activates orexin-containing neurons in the hypothalamus and enhances histaminergic neurotransmission in the hypothalamus (Ishizuka et al., 2003). Moreover, modafinil is a weak but very selective DAT inhibitor. Furthermore, there was a greater improvement in hypersomnia scores among bupropion-treated than SSRI-treated depressed patients, suggesting the involvement of a noradrenergic and/or dopaminergic component in hypersomnia (Papakostas et al., 2006).

3.2.6. Interpersonal rejection or inappropriate guilt

Feelings of worthlessness, rejection or guilt as well as cognitive dysfunction, including concentration problems and problem-solving disabilities, are all linked to malfunctioning of the PFC and regulated by multiple neurotransmitters projecting to the PFC (Rypma and D'Esposito, 1999; Li et al., 2004). It is expected that similar areas, which are responsible for depressed mood (Section 3.2.1), are also involved in cognitive dysfunction. However, as the functions of the PFC and surrounding cortical areas rely closely on connections with a lot of other neuronal structures, none of its cognitive functions can be fully understood if taken out of context of its wide-ranging networks (see also Fig. 2) (Fuster, 1991, 2000, 2001).

3.3. Personalized medicine in major depression with atypical features

In atypical depression, symptoms as fatigue, psychomotor retardation and decreased sympathetic activity can be mainly attributed to disturbances in dopaminergic and noradrenergic systems. Prolonged stress or pain is known to result in increased tonic dopamine levels, which will result in an attenuated phasic dopamine response (see also Fig. 8) (Wood, 2006). Here it is hypothesized that in atypical depression, the dopamine transporters and receptors are down regulated due to increased tonic dopamine levels, thereby decreasing capacity of the system to regulate dopaminergic signaling. Dopaminergic pathways are involved in reward and hedonic processes, thereby hypothetically affecting paradoxical anhedonic symptoms in depression (Nestler and Carlezon, 2006; Dunlop and Nemeroff, 2007; Nutt et al., 2007; Guiard et al., 2009).

There is a large body of evidence that atypical depression is associated with increased immune activity, reflected by increased proinflammatory cytokine concentrations that affect brain monoamine functioning, not only of dopamine, but also of norepinephrine and 5-HT (van Heesch et al., 2013a, 2013b, 2014; Penninx et al., 2013). During chronic inflammation increased levels of proinflammatory cytokines can affect the emotional brain via different routes. For example:

1) increased levels of indoleamine 2,3-dioxygenase (IDO) are responsible for lower tryptophan levels and consequently lower serotonin levels in the brain (Dantzer et al., 2008; O'Connor et al., 2009; Raison and Miller, 2013; Lopresti et al., 2014; Felger and Miller, 2014). Interestingly, already in the seventies it was shown that carbohydrate intake could increase brain serotonin content, thus sugar craving in atypical depressed persons can be seen as a short-term adaptive behavioral response (Fernstrom and Wurtman, 1971; Wurtman and Wurtman, 1995);
2) due to an increase in reactive oxygen species (ROS) the availability of the co-factor BH4 will decrease, since BH4 stimulates the rate-limiting enzymes (tryptophan-hydroxylase and tyrosine-hydroxylase) for the synthesis of monoamines, both serotonin, melatonin, dopamine and norepinephrine will decrease (Shelton and Miller, 2010; Felger and Miller, 2014; Sperner-Unterweger et al., 2014);
3) increased levels of pro-inflammatory cytokines stimulate the p38 MAPK pathway and MEK pathway, thereby enhancing SERT, DAT and NET trafficking and function, respectively (Blakely et al., 2014; Capuron et al., 2012; Felger et al., 2013; Gowrishankar et al., 2014; Miller et al., 2013; Morón et al., 2003; van Heesch et al., 2013a, 2013b, 2014; Zhu et al., 2006, 2007, 2010);
4) and finally, the immune response can affect the nervus vagus, and thereby decreasing parasympathetic activity (Bulloch and Pomerantz, 1984; Tracey, 2002; Pavlov and Tracey, 2005). In addition, it has been shown that nervus vagus stimulation can be successfully applied both to reduce inflammation and major depression.

Knowing that the above described mechanisms together result in a decrease in monoamines, it is not surprising that drugs that increase all monoamines (Willner, 1997; Goldberg et al., 2004; Gupta et al., 2006; Trivedi et al., 2006) are more successful in treating the disease

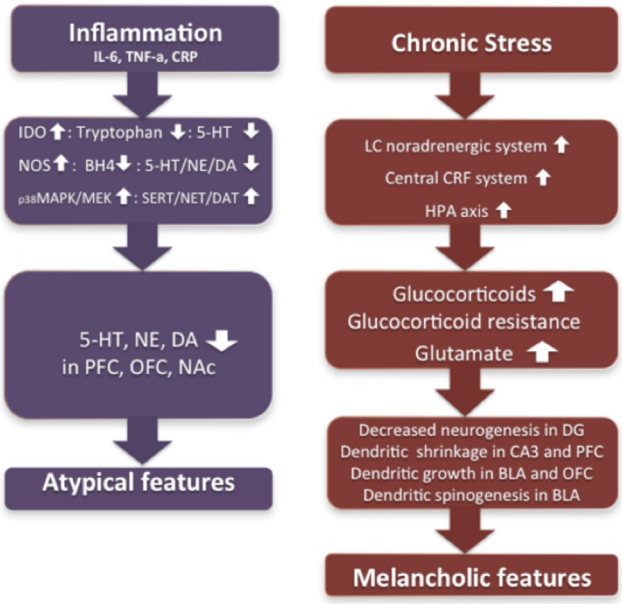

Fig. 8. Neurobiological mechanisms by which inflammation affects monoamine levels and consequently atypical features of major depression and how chronic stress affects both glucocorticoid and glutamate levels leading to altered neuroplasticity and consequently melancholic features of depression.

symptoms. Drugs acting on all three monoamine neurotransmitter systems simultaneously should hypothetically cover a larger range of depressive symptoms (Guiard et al., 2009), but potentially also will have more side effects! Furthermore, it is expected that TRIs, and also MAOIs, are especially effective in atypical depression because they increase all three monoamine concentrations, but with a better safety profile (see Fig. 8) (Axelrod et al., 1961; Thase et al., 1992, 1995). Although MAO inhibitors have a bad reputation, with dietary restrictions and potential drug interactions with 5-HT and norepinephrine agents, the newer MAO inhibitors (e.g. selegiline in a transdermal patch) represent a currently available and safer "secret weapon" that provides triple reuptake inhibition (Shulman et al., 2013). However, more research is needed before definitive recommendations can be made. Another potential drug combination expected to be effective in atypical depression is for instance escitalopram together with bupropion. Also this approach needs more research.

3.4. Personalized medicine in major depression with melancholic features

Melancholic depression is associated with a hyperactive CRF system and HPA axis; thereby glucocorticoid receptors are down-regulated and lead to feedback resistance; consequently, hypersecretion of glucocorticoids further increases and may decrease neuroplasticity in frontal cortex, PFC and hippocampus, for example, neurogenesis in the dentate gyrus, dendritic remodeling in the CA3 region of the hippocampus (Sapolsky, 2000; McEwen, 2001). Chronic exposure to glucocorticosteroids may even cause a selective loss of hippocampal volume and neuron loss due to allostatic load (Sapolsky, 2000). Remarkably, previously it has been shown that a MAO-A inhibitor produces an increase in brain corticosteroid receptors, suggesting that glucocorticoid receptor-mediated feedback can be restored by antidepressants (Reul et al., 1994). It has been shown that different paradigms of stress or corticosteroid administration induce a rapid and transient increase in extracellular glutamate in PFC and hippocampus (Moghaddam et al., 1994; Stein Behrens et al., 1994; Venero and Borrell, 1999). Moreover, it has been shown that acute stress may rapidly increase the level of circulating corticosteroids that, by binding to membrane-located mineralocorticoid receptors and rapid non-transcriptional action, induces the release of glutamate in hippocampus (Karst et al., 2005; Olijslagers et al., 2008) and by binding to glucocorticoid receptors, induces the release of glutamate in PFC and frontal cortex (Yuen et al., 2009; Musazzi et al., 2010). If new monoaminergic antidepressants, including TRIs, can dampen states of hyperglutamatergic activity and the subsequent excitotoxicity, their chronic use may have a considerable neuroprotective potential in major depression, especially melancholic depression (Michael-Titus et al., 2000).

In melancholic depression, a highly active stress system causes a hyperactive noradrenergic system (Wong et al., 2000a). Furthermore, symptoms of anxiety in melancholic depression are associated with increased serotonergic neurotransmission, whereas dopaminergic neurotransmission is often decreased and responsible for feelings of anhedonia. The alterations in norepinephrine and 5-HT, however, cannot be explained as simply increased or decreased neurotransmitter availability. In our view, the pathophysiology of depression should make a distinction between the "state" of a diseased brain or a healthy brain. It is more accurate to hypothesize that in major depression, neurotransmission is "out of tune", rather than deficient (see Fig. 9).

For example, normal neurotransmission can be explained as a balance between tonic levels of extrasynaptic monoamines that are present at steady-state concentrations in the synaptic cleft and phasic monoamine bursts in response to neuronal firing (Schultz, 2007, 2010). For example, when tonic monoamine levels are high, the phasic monoamine response will be attenuated (Floresco et al., 2003; Schultz, 2007), whereas low tonic monoamine levels facilitate phasic 5-HT postsynaptic functioning (Grace, 1991; Leknes and Tracey, 2008). In melancholic depression, the tonic "resting state" of 5-HT in the brain may be increased compared with a healthy brain. It is speculated that stress and increased serotonergic neurotransmission lead to down regulated postsynaptic 5-HT receptors (Korte et al., 1995), whereas 5-HT transporters are up regulated. This new allostatic state can be interpreted as an ultimate attempt to stabilize the serotonergic system. Increased brain norepinephrine and 5-HT concentrations can also be interpreted as an adaptive response to counteract the damaging brain effects of glucocorticoids (see Fig. 9), because both 5-HT as well as norepinephrine increases the genetic expression of growth factors such as BDNF, which results in increased neuroplasticity in hippocampus and PFC (Duman, 2004).

When melancholic depression is treated with SSRIs or SNRIs, an acute phasic response in 5-HT and or norepinephrine levels is present, which produces immediate adverse side effects (e.g., anxiety), but longterm treatment also positively affects neuroplasticity in the PFC (Duman, 2004). Moreover, agitation and an increased sympathetic activity in melancholic depression are associated with high phasic norepinephrine response. So in melancholic depression, the capacities of these two monoamine systems are high and drugs that can normalize these disturbed neurotransmission pathways may have the highest probability of success to relieve symptoms.

In melancholic depression, especially chronic stress processes and chronic elevations in both glucocorticoid levels and brain glutamate play an important role in the disease development. Although there have been many efforts with corticosteroid receptor antagonists or CRF receptor antagonists in clinical trials to treat depression, until now it has been shown difficult to beat SSRIs or SNRIs. But there may be new antidepressants on the horizon. The drug ketamine, a glutamate N-methyl-D-aspartic acid (NMDA) receptor antagonist, has a fast antidepressant effect within 24 h (Berman et al., 2000; Lapidus et al., 2014). Thus, NMDA receptor antagonists seem to address the limitations of currently available SSRIs or SNRIs, such as slow-onset and relatively treatment resistance. It is thought that this fast antidepressant effect is produced by rapid induction of synaptogenesis and spine formation in the PFC via stimulation of an mTOR-dependent pathway

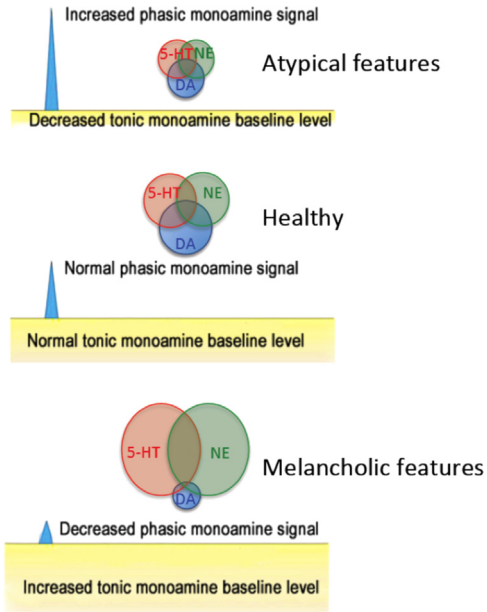

Fig. 9. It is hypothesized that in major depression with atypical features there are decreased tonic monoamine levels in the brain as compared to a healthy brain and consequently there is an increased phasic monoamine signal. In contrast, in major depression with melancholic features there are supposed to be increased tonic monoamine levels in the brain (except for dopamine) as compared to a healthy brain and consequently there is a decreased phasic monoamine signal. Figure inspired by: Floresco et al. (2003).

(Li et al., 2010; Duman and Li, 2012). Ketamine's limiting factors are the transient nature of its antidepressant effect, side effects such as hallucinations, and concerns regarding abuse. More research and clinical trials are needed, to investigate whether NMDA receptor antagonists will become first-choice drugs for "treatment-resistant" melancholic depression in the near future.

4. Conclusions

An improved treatment of major depression should start with a better diagnosis, based on the different features present in major depression (see DSM-5, Association of American Psychiatry, 2013). In the present review, we clearly show that in major depression, e.g. with atypical or melancholic features, different neuropsychopathological mechanisms may be responsible for the different symptoms. Therefore, different faces of depression need personalized treatments.

In atypical depression it is crucial to investigate whether inflammation is involved (e.g. high levels of CRP). One also has to be aware that patients who suffer from a rheumatologic disorder, cardiovascular disease, Crohn's disease, psoriasis, or diabetes mellitus etc. have a much higher risk to develop major depression with atypical features, because they may have increased levels of proinflammatory cytokines, that disturb brain functioning, including a general increased monoamine metabolism. Thus, the increased state of inflammation has to be treated first, for example with NSAIDs or other anti-inflammatory drugs. Interestingly, there is a growing body of evidence that shows that SSRIs are also able to decrease proinflammatory cytokine levels (Hernandez et al., 2013). In addition, most effective treatments for atypical depression are MAO inhibitors or SSRI combined with DNRI (off-label prescription), because these treatments increase all three monoamines levels.

In melancholic depression it is crucial to investigate whether there is increased HPA axis activation and increased cortisol levels (and feedback resistance). This condition is often associated with more generalized anxiety with higher glutamate levels in the emotional brain, which negatively affects neuroplasticity. Psychotherapy can be effective in treating the anxiety, while SSRIs or SNRIs positively affects the above-mentioned neuroplasticity and other symptoms.

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