Neurochemical Imaging and Depressive Behaviours

Jeffrey H. Meyer

Abstract Neurochemical imaging is frequently applied to measure markers of pathological change so as to understand mechanisms that create symptoms of major depressive disorder. For example, indices of greater monoamine oxidase A(MAO-A) level, particularly in the prefrontal and anterior cingulate cortex, are associated with depressed mood states, and high-risk states for onset of major depressive episodes. MAO-A metabolises monoamines, and greater metabolism of monoamines occurs when MAO-A is elevated in brain. Lower extracellular serotonin is associated with greater pessimism in humans and chronic serotonin deficiency is associated with upregulation of 5-HT_{2A} (serotonin$_{2A}$) receptors in cortex. During major depressive episodes when pessimism is more severe, greater 5-HT_{2A} BP_{ND}, an index of density occurs in prefrontal and anterior cingulate cortex. These results argue for a mechanism of lowering extracellular serotonin in the prefrontal and anterior cingulate cortex, consequent to elevated MAO-A level. The relationship between elevated 5-HTT BP_{ND} and greater pessimism during major depressive episodes suggests that greater 5-HTT density in the context of elevated MAO-A level further contributes to serotonin deficiency in these brain regions. A similar mechanism may explain the association between neuroimaging indices of greater dorsal striatal D_2 density, DAT density and symptoms of motor retardation: Greater MAO-A level and relatively greater DAT density lower extracellular dopamine in the dorsal striatum, leading to motor retardation. Indices of greater 5-HT_{1A} density,

J. H. Meyer (✉)
Department of Psychiatry, University of Toronto, Toronto, Canada
e-mail: jeff.meyer@camhpet.ca

J. H. Meyer
Canada Research Chair in Neurochemistry of Depression Head,
Neurochemical Imaging Program in Mood Disorders Centre for Addiction
and Mental Health Research Imaging Center, Toronto, Canada

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particularly in the cingulate cortex, have been associated with major depressive disorder, and well as anxiety disorders, suggesting that this abnormality is mechanistically related to presence of anxiety symptoms. To date, abnormalities of Glx a measure reflecting glutamate and glutamine levels have been most strongly associated with presence of major depressive episodes, with greater levels in occipital cortex, and reduced levels in prefrontal cortex. Ultimately, the future for neurochemical imaging is to better understand the mechanisms that predispose toward onset of MDE so as to create biologically informed, novel, methods of prevention, and superior, more symptom-targeted treatments.

Keywords Monoamine oxidase A · Serotonin$_{2A}$ receptors · Serotonin transporter · Serotonin$_{1A}$ receptors · Dopamine$_2$ receptors · Dopamine transporter Glutamate · Major depressive disorder

Contents

1 Introduction

Major depressive disorder affects 2–5 % of the population at any time and is the third leading cause of death and disability, according to the world health organisation (World Health Organization 2008). Given its high prevalence an important issue is to better understand the aetiology of symptoms so as to develop new strategies for prevention and more targeted approach for treatment.

Neurochemical imaging techniques offer an opportunity to measure markers of neurophysiological change to better understand mechanisms that contribute toward

onset of symptoms during major depressive disorder. By identifying neurochemical abnormalities of MAO-A level, 5-HT_{2A} (serotonin$_{2A}$), 5-HTT (serotonin transporter), 5-HT_{1A} (serotonin$_{1A}$), D_2, DAT as well as glutamate levels in functionally important regions, then relating these findings to symptoms, and illness state, neuroimaging investigations are making important contributions toward understanding the pathophysiology of major depressive disorder.

2 Monoamine Oxidase A and Depressed Mood

2.1 Monoamine Oxidase A, Monoamines and Mood

Monoamine oxidase-A (MAO-A) is an enzyme with diverse functions in the brain, some of which have important roles for influencing mood; for most brain tissues, MAO-A activity is the main route for serotonin metabolism, and a significant route of metabolism for other monoamines, including norepinephrine and dopamine (Youdim et al. 2006). MAO-A is detectable in cells that release these monoamines, with the highest levels in norepinephrine releasing neurons (Konradi et al. 1988, 1989; Luque et al. 1995; Moll et al. 1990; Saura et al. 1996); however, MAO-A is also present in cells that do not release monoamines, such as astrocytes and glia (Youdim et al. 2006). Within cells, MAO-A is mainly located on outer mitochondria membranes. MAO-A has a high density in brain regions that influence mood (Saura et al. 1992): While MAO-A density is highest in brainstem (within the locus coeruleus), it is moderately high in the cortex, hippocampus, striatum, much lower in cerebellar cortex and minimal in white matter tissue. In addition, MAO-A has pro-oxidant effect, via the production of hydrogen peroxide, and is functionally linked to apoptosis. The latter is based on the observations that MAO-A inhibitors reduce apoptosis and MAO-A expression is increased in cell lines that are in a pro-apoptotic state (Ou et al. 2006). Among these roles, it is the effect of MAO-A upon monoamine metabolism that is highly implicated in influencing mood state.

There is a considerable amount of data linking loss of extracellular serotonin, norepinephrine and dopamine in humans with onset of depressed mood and/or major depressive episodes. Overall, two temporal mechanisms have been observed, one acute and one chronic. For example, acute monoamine depletion, through either tryptophan depletion to lower brain serotonin or alpha-methyl-para-tyrosine to lower brain dopamine and norepinephrine, is associated with depressed mood (Freis 1954; Hasler et al. 2008; Neumeister et al. 2004b; Verhoeff et al. 2001; Young et al. 1985). The second type of mechanism observed is that long periods of monoamine depletion are associated with onset of MDE in humans as demonstrated by chronic reserpine administration (Freis 1954).

In brain tissue, the density of MAO-A correlates highly with the level of its metabolic activity. Thus, given the functional link between monoamine loss and low mood and/or MDE, and the role of MAO-A in metabolising multiple monoamines,

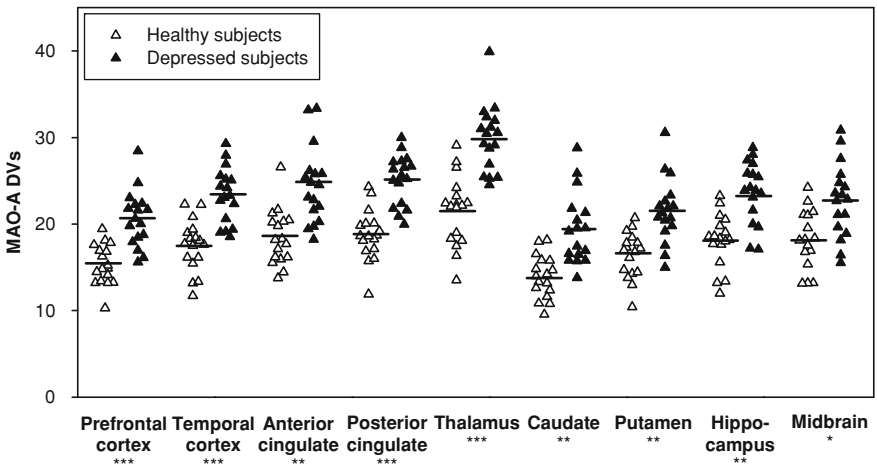

Fig. 1 Comparison of MAO-A DV_s between depressed and healthy subjects. On average MAO-A DV_s was elevated by 34 percent, or two standard deviations, in depressed individuals. Differences between groups were highly significant in each region: * p=0.001, ** p<0.0001, *** p<0.00001. Reprinted from Meyer et al. (2006a)

states that raise of MAO-A level in affect modulating brain regions would be expected to influence overall mood toward a depression. Additional evidence for a relationship between MAO-A and mood has been that one longstanding class of antidepressants, MAO inhibitors, has been effective treatments; this provides another reason to investigate this target in depressed mood states (Youdim et al. 2006). The relationship between MAO-A density and depressed mood may now be tested: recent advances in positron emission tomography (PET) neuroimaging such as [^{11}C]harmine PET enable optimal quantitation of MAO-A V_T, a measurement proportional to MAO-A density.

2.2 Prefrontal and Anterior Cingulate Cortex Monoamine Oxidase A Binding, Depressed Mood and Major Depressive Disorder

A key advantage of neuroimaging for investigating major depressive episodes (MDE) is that the in vivo measurement of MAO-A V_T may be conducted in medication free subjects and in the specific grouping of early onset MDD. Most MDD is related to early onset, and it vital to differentiate early from late onset for investigations of MDD, because late onset MDD is associated with neurodegenerative disease such as Parkinson's disease or Alzheimer's disease, which can be viewed as different pathologies. The issue of selecting early onset medication free subjects was not readily addressable in the first three postmortem studies of MAO-A levels and/or activity, hence prior to 2006 it was unknown whether MAO-A

density or activity was increased in early onset major depressive disorder. In 2006, MAO-A V_S, an index of MAO-A density, was measured using [^{11}C] harmine PET in medication free MDE secondary to early onset MDD (Meyer et al. 2006a). Subjects with MDE were drug free for at least 5 months and most were antidepressant naive. All MDE subjects and controls were otherwise healthy. The MAO-A V_S was highly significantly elevated ($p < 0.001$ each region, average magnitude 34 % (or two standard deviations)) during MDE (see Fig. 1). This was the first definitive study of MAO-A binding in MDE because the clinical sample was carefully defined to focus upon MDD, the effect size was large and the PET radiotracer [^{11}C] harmine has outstanding qualities for measuring MAO-A binding.

Later studies have been highly consistent in support of this finding: Barton et al. (2008) reported elevated brain serotonin turnover in unmedicated depressed patients, a phenomenon which could be explained by greater brain MAO-A level (Barton et al. 2008). In 2009, the finding of greater MAO-A binding in MDE was replicated with [^{11}C] harmine PET in the same laboratory, and in 2011 the finding was replicated in antidepressant free MDE subjects in postmortem study of orbitofrontal cortex in a different laboratory applying Western blot (Johnson et al. 2011; Meyer et al. 2009).

Monoamine lowering processes may lead to lowered mood, hence, in recovery from MDD, it might be expected that MAO-A levels would normalise with euthymic mood. However, the recovered state of MDD is also a state of high risk for another MDE. The risk for a recurrent MDE over 2 years is 20–50 % depending upon treatment conditions. Elevated MAO-A binding may be considered an index of a monoamine lowering process and in the 1950s during treatment with reserpine-based antihypertensives, it was discovered that chronic monoamine lowering is associated with subsequent onset of MDEs which typically occurred 2 weeks to 4 months later (Meyer et al. 2009). The in vivo nature of neuroimaging enabled measurement of MAO-A V_T, an index of MAO-A density, in a study of recovered MDD. In this study, MAO-A binding was significantly elevated in prefrontal cortex, anterior cingulate cortex, striatum, hippocampus, thalamus and midbrain in a sample of 18 medication free recovered MDD subjects compared to 28 healthy controls (Meyer et al. 2009). Recovered MDD subjects who had recurrence of their MDE in the subsequent 6 months had the highest levels of MAO-A binding in the prefrontal and anterior cingulate cortex at the time of scanning (Meyer et al. 2009). The prefrontal cortex and anterior cingulate cortex were prioritised because these regions (and/or subregions of these structures) are often activated in mood induction studies (reflecting processes that generate sad mood) (Liotti et al. 2002) and these regions participate in cognitive functions like pessimism which create sad mood (Sharot et al. 2007; Tom et al. 2007). In this MDD sample (Meyer et al. 2009), other factors related to recurrence were accounted for: Subjects were medication free for at least 1 year, had no cognitive behavioural therapy within 3 years, were currently asymptomatic, and had no comorbid medical, psychiatric or substance abuse illnesses. Given the link between elevated MAO-A binding in prefrontal and anterior cingulate cortex and subsequent MDE, a stronger case can be made that new therapeutics are needed to decrease MAO-A levels in these brain regions, ideally with persistence beyond the duration of administration of the therapeutic to prevent recurrence.

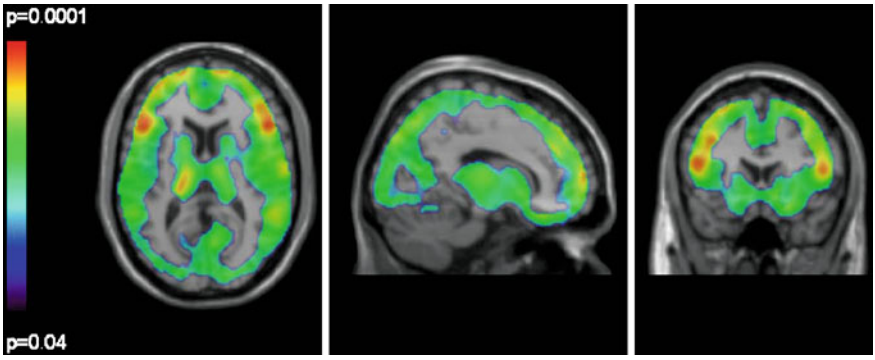

Fig. 2 Regional distribution of p-values reflecting elevated MAO-A binding in immediate postpartum period. Parametric maps of elevated monoamine oxidase A binding in the postpartum group vs the control group. Maps are superimposed on a T1-weighted magnetic resonance image that is normalized to the T1-weighted template (SPM2; Department of Cognitive Neurology, Wellcome Trust Centre for Neuroimaging, London, UK). **a** Transverse. **b** Sagittal. **c** Coronal. Individual voxel threshold was set at $P<0.05$; 86 412 voxels comprised a single cluster, which had a cluster-corrected significance of $P=0.03$. Mean regional difference was 43%

2.3 Monoamine Oxidase A and Depressed Mood During Postpartum

Depressed mood is common during early postpartum and can be categorised into three different syndromes. One common syndrome, occurring up to 75 % of the time, and considered within the healthy range of experience, is the "baby blues" or maternity blues. This consists of sad mood typically peaking on day 5 and ending with the first week postpartum accompanied by some irritability, desire to be alone, insomnia and trouble concentrating (O'Hara and Swain 1996). The second syndrome, which is also common with a prevalence rate of 13 %, is a full, clinical level MDE occurring within the first 1–3 months after delivery (O'Hara and Swain 1996; American Psychiatric Association 1994). The third syndrome, postpartum psychosis, is relatively rare with a prevalence rate of 0.1–0.2 %, and includes a combination of a MDE with hallucinations or delusions (Brockington et al. 1981; Kendell et al. 1987).

The first investigation of MAO-A in the postpartum period occurred in 2010: A [^{11}C] harmine PET study measured MAO-A V_T during postpartum blues (with scanning done between days 4 and 6 postpartum). A highly significant elevation of MAO-A binding was found, which, on average, was 43 % greater across the brain regions assayed (prefrontal cortex, anterior cingulate cortex, striatum, thalamus, hippocampus and midbrain) as compared to women not recently pregnant (Sacher et al. 2010). A voxel-based analysis demonstrated that the elevation in MAO-A binding was present throughout the grey matter of the brain (see Fig. 2) (Sacher et al. 2010).

This discovery led to a new neurobiological explanation for postpartum blues, involving a rapid decline in estrogen, followed by a rapid rise in MAO-A levels in affect-modulating brain regions, and finally subsequent sad mood with postpartum blues. During pregnancy, estradiol and estriol levels rise more than 100-fold and during the first week postpartum, with loss of the placenta, there is an enormous reduction in 17β-estradiol and estriol levels (O'Hara et al. 1991). Most of the decline in estrogens occur in the first 4 days followed by a more modest decline thereafter (O'Hara et al. 1991). Although MAO-A had never been previously investigated in the postpartum, it is known that estrogen decline is associated with a rise in either MAO-A density, activity or mRNA (see review (Sacher et al. 2010)). The 43 % elevation in MAO-A V_T in early postpartum confirms that this inverse relationship is applicable to the early postpartum period, after the early estrogen decline. MAO-A V_T can be viewed as an index of MAO-A levels and MAO-A levels correlate highly with MAO-A activity in brain tissue (Saura et al. 1992). Hence, the acute rise in MAO-A V_T in the early postpartum period represents a monoamine-lowering process and acute monoamine lowering processes are associated with sad mood (Ruhe et al. 2007).

2.4 Cigarette Withdrawal, Depressed Mood and MAO-A

Sad mood is an important problem for people who smoke cigarettes. First, during early withdrawal, sad mood frequently occurs, and when sad mood is prominent during withdrawal, it is associated with greater likelihood of relapse during quit attempts (Carey et al. 1993; Kenford et al. 2002). Second, cigarette smoking predisposes to MDD and vice versa; consequently, there is a very high comorbidity between cigarette smoking and major depressive disorder with 50 % of people with MDD also smoking cigarettes (Anda et al. 1990; Breslau et al. 1998).

The initial impression of the neuroimaging field was that MAO-A binding is reduced in those who smoke cigarettes in the active smoking state (Fowler et al. 1996). Given that, the plasma half-life of the key MAO-A binding substances found in cigarette smoke (harman and norharman) is only an hour (Rommelspacher et al. 2002), there was reason to specifically assess MAO-A V_T during both active smoking and withdrawal conditions. When MAO-A V_T was assessed in both conditions, it was discovered that prefrontal and anterior cingulate cortex MAO-A V_T rose during withdrawal in those who smoke heavily, that is, more than one pack of cigarettes per day, but not in those who smoke more moderately at less than one pack per day (see Fig. 3 from Bacher et al. (2011)). Interestingly, it is the heavy cigarette smoking group who are known to be at much greater risk for MDD (Pratt and Brody 2010), and it was this group that had 25 % elevated MAO-A V_T in the prefrontal and anterior cingulate cortex during withdrawal as compared to healthy controls, arguing for a process of elevated MAO-A level during withdrawal as a mechanism to create risk for MDD. Hence repeated exposure of elevated MAO-A level, in the prefrontal and anterior cingulate cortex, a mechanism associated MDD,

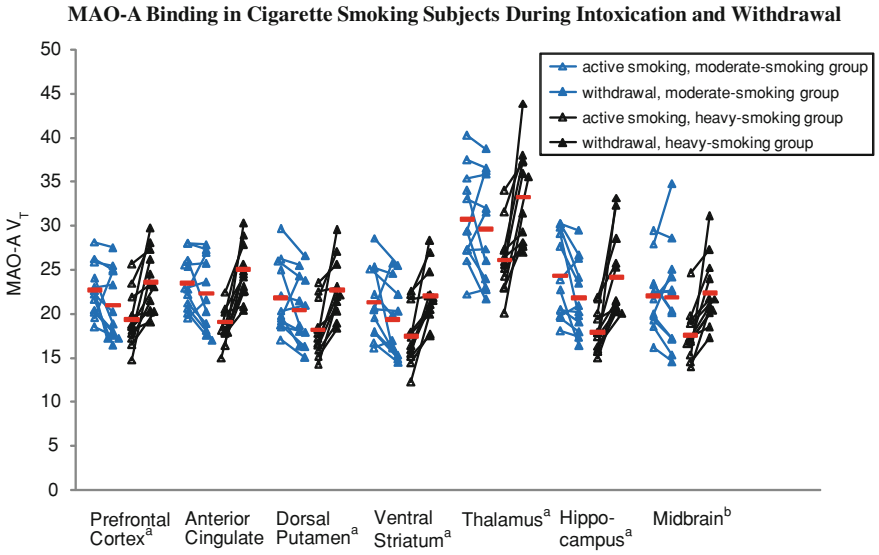

Fig. 3 Monoamine Oxidase-A binding in cigarette smoking subjects during active smoking and withdrawal. Repeated measures MANOVA found a highly significant effect between smoking severity and change in MAO-A V_T in the prefrontal cortex and anterior cingulate cortex regions ($F_{1, 22} = 25.58$, $p<0.001$). Repeated measures MANOVA also found a significant effect between smoking severity and change in MAO-A V_T for all the regions assayed ($F_{1, 22} = 28.24$, $p<0.001$). The effect was confirmed in each region with a repeated measures ANOVA (interaction between smoking severity and change in MAO-A V_T, repeated measures ANOVA, $F_{1, 22} = 11.16$ to 28.87, $p = 0.003$ to $p<0.001$). [a] $p<0.001$ [b] $p = 0.003$. Greater MAO-A binding during acute cigarette withdrawal in heavy smoking group compared with healthy (MAO-A VT within groups were compared with an independent t-test. a $p \leq 0.001$ b $p \leq 0.005$ c $p \leq 0.01$ d $p \leq 0.05$ e $p \leq 0.1$ Arch Gen Psych (in press))

occurring after a short period of 8 h withdrawal could explain the predisposition to MDD in people who smoke cigarettes heavily.

As mentioned earlier, a second problem with mood in people who smoke cigarettes is the depressed mood of acute withdrawal (Carey et al. 1993; Kenford et al. 2002). In the imaging study of MAO-A during cigarette withdrawal, those who smoked heavily, the magnitude of rise in MAO-A V_T in prefrontal and anterior cingulate cortex during withdrawal was significantly correlated with the shift in visual analogue scales toward depressed mood (Bacher et al. 2011). This rise in MAO-A V_T also correlated with the decline in the MAO-A binding substance harman in those who smoke heavily. These results have significant implications for quitting heavy smoking. They suggest that rapid removal of harman from occupying MAO-A sites leaves a high level of available MAO-A for metabolising monoamines in prefrontal and anterior cingulate cortex resulting in depressed mood. This argues for testing of MAO-A inhibitor treatments in people who experience sad mood during early cigarette withdrawal as a strategy to assist

in quitting, an important issue since 50 % of people tend to relapse in the first few days of trying to quit cigarette smoking (Garvey et al. 1992; Law and Tang 1995).

In conclusion, greater MAO-A V_T occurs, particularly in the prefrontal and anterior cingulate cortex, in a number of low mood states that are also associated with predisposition to major depressive disorder (Bacher et al. 2011; Meyer et al. 2009; Sacher et al. 2010). This data has major implications for preventing major depressive disorder as it suggests that better understanding and regulation of MAO-A may be helpful in avoiding the onset of major depressive episodes.

3 Pessimistic Perspective, 5-HT_{2A} Receptor and 5-HTT Receptor Imaging

3.1 5-HT_{2A} Receptor Imaging in Prefrontal and Anterior Cingulate Cortex

Negativistic thinking often occurs during major depressive episodes and it is important because high levels of hopelessness, a key component of pessimism, are associated with greater risk of suicide. Pessimism during major depressive episodes has also been captured by the concept of 'dysfunctional attitudes'. While a modest level of dysfunctional attitude can viewed as adaptive, dysfunctional attitudes increase significantly during major depressive episodes (Simons et al. 1986; Weissman 1979). Greater pessimism during major depressive episodes contributes to negative thoughts, and subsequent sad mood and this underlying pessimism is targeted by cognitive therapy (Simons et al. 1986; Weissman 1979). Dysfunctional attitudes may be measured with the dysfunctional attitudes scale (DAS), a measure that is sensitive for detecting negativistic thinking during major depressive episodes (Simons et al. 1986; Weissman 1979), and also demonstrates very good internal consistency (Cronbach alpha = 0.85–0.87) (Cane et al. 1986; Oliver and Baumgart 1985) and has high test–retest reliability (Oliver and Baumgart 1985; Weissman 1979).

Two findings initially suggested a relationship between manipulations of extracellular serotonin and dysfunctional attitudes. The first is that dysfunctional attitudes normalise during the response to selective serotonin reuptake inhibitor (SSRI) treatment (Fava et al. 1994; Simons et al. 1986). The second is that raising extracellular serotonin after administration of intravenous d-fenfluramine rapidly shifts dysfunctional attitudes toward optimism in healthy individuals (Meyer et al. 2003). These results argue that one of the roles of serotonin is to modulate dysfunctional attitudes in humans. More recently, the rostral anterior cingulate cortex and subregions of prefrontal cortex (dorsolateral, and medial prefrontal cortex) have been demonstrated to participate in functions related to optimism and pessimism (Elliott et al. 2002; Sharot et al. 2007).

Direct evidence that serotonin is low in brain is difficult to obtain: Brain serotonin cannot be directly measured in vivo and it is likely, based upon animal simulations of postmortem delay, that serotonin levels are very unstable, even within 24 h of death (Kontur et al. 1994). Moreover, postmortem investigations reviewed by Mann et al. (1996), Stockmeier (2003) have difficultly sampling medication free subjects.

While one cannot measure extracellular serotonin directly during major depressive episodes with neuroimaging either, one may measure an index of regional 5-HT_{2A} receptor density such as 5-HT_{2A} BP or 5-HT_{2A} BP_{ND} (an index of specific binding relative to free and non-specific binding). 5-HT_{2A} density has an inverse relationship to extracellular serotonin such that binding increases when extracellular serotonin is chronically lowered (O'Regan et al. 1987; Roth et al. 1987; Stockmeier and Kellar 1986; Todd et al. 1995). Therefore, if extracellular serotonin loss occurred in the prefrontal and anterior cingulate cortex during MDE, increased 5-HT_{2A} BP_{ND} would occur in these regions. A review of the initial set of 5-HT_{2A} imaging studies of MDE find a reduction in those with recent antidepressant use, and no change in those with no recent antidepressant use (see Table 1) (Meyer 2008). One could interpret the reductions in 5-HT_{2A} binding in recently treated subjects as being consequent to recent antidepressant use. The other set of findings, reflecting the medication free state of MDE, which found no change in 5-HT_{2A} BP_{ND} would suggest either abandoning the notion of reduced extracellular serotonin in the prefrontal and anterior cingulate cortex during MDE or creating an alternative hypothesis.

One alternative perspective is that monoamine loss during MDD is heterogenous and that the loss is greatest in those with the most severe symptoms. The first investigations of this revision began with prefrontal cortex 5-HT_{2A} BP_{ND} measurement and its relationship to dysfunctional attitudes. A strong correlation was observed between severity of dysfunctional attitudes (pessimism) and elevation in prefrontal and anterior cortex 5-HT_{2A} BP_{ND}. Furthermore, cortex 5-HT_{2A} BP_{ND} was significantly elevated in subjects with MDE and severe pessimism (Meyer et al. 2003). For example, in the prefrontal cortex region of interest centred on Brodman's area 9, 5-HT_{2A} BP_{ND} was elevated 29 % in depressed subjects with dysfunctional attitude scores greater (more pessimistic) than the median for the group. There was also a strong, significant correlation between severity of pessimism and prefrontal cortex 5-HT_{2A} BP_{ND} (see Fig. 4). A study by Bhagwagar et al. replicated this relationship between dysfunctional attitudes severity and prefrontal cortex 5-HT_{2A} BP_{ND} in recovered depressed subjects(Bhagwagar et al. 2006). In another study of a large sample of healthy subjects, two personality factors related to pessimism, vulnerability and anxiety, also positively correlated with prefrontal cortex, temporal cortex and left insula 5-HT_{2A} BP_{ND} (Frokjaer et al. 2008).

These results provide an explanation to interpret the investigations of suicide victims which had been a key focus of the mood disorders field between the mid 1984 and 2000. At that time, the most consistent postmortem biological abnormality in suicide victims was increased serotonin$_{2A}$ receptor density in the prefrontal cortex, most commonly in Brodmann's area 9 (Arango et al. 1990, 1992; Arora and Meltzer 1989; Hrdina and Vu 1993; Mann et al. 1986; Pandey et al. 2002; Stanley

Table 1 Imaging studies of 5-HT_{2A} receptors in major depressive disorder [updated from Meyer (2008)]

Study	Method	Number of subjects	Medication free status	Result
D'Haenen et al. (1992)	[^{123}I] ketanserin SPECT	19 Depressed 10 Healthy	7 days	Greater in parietal cortex
Biver et al. (1997)	[^{18}F]altanserin PET	8 Depressed 22 Healthy	10 days	Lower in orbitofrontal cortex
Attar Levy et al. (1999)	[^{18}F] setoperone PET	7 Depressed 7 Healthy	Taking benzodiazepines	Lower in prefrontal cortex
Meyer et al. (1999)	[^{18}F] setoperone PET	14 Depressed 14 Healthy	3 months plus 5 half lives	No difference
Meltzer et al. (1999)	[^{18}F] altanserin PET	11 Depressed 11 Healthy	"untreated"	No difference
Yatham et al. (2000)	[^{18}F] setoperone PET	20 Depressed 20 Healthy	2 weeks	Decrease in all cortex
Messa et al. (2003)	[^{18}F] setoperone PET	19 Depressed 19 Healthy	Taking benzodiazepines	Decrease in all cortex
Meyer et al. (2003)[a]	[^{18}F] setoperone PET	22 Depressed 22 Healthy	6 months	Positive association with dysfunctional attitude severity in cortex
Mintun et al. (2004)[b]	[^{18}F]altanserin PET	46 Depressed 29 Healthy	4 weeks	Decrease in hippocampus
Bhagwagar et al. (2006)	[^{11}C] MDL100907	20 Recovered Depressed 20 Healthy	6 months	Positive association with dysfunctional attitude severity in prefrontal cortex; elevation in most cortex regions

[a] Subjects enroled in the study by Meyer et al. (1999) were also included in the expanded study by Meyer et al. (2003) of 5-HT_{2A} receptors and dysfunctional attitudes in subjects with depression as well as subjects with borderline personality disorder

[b] Findings appear largely driven by a single healthy subject with very high 5-HT_{2A} BP_{ND}

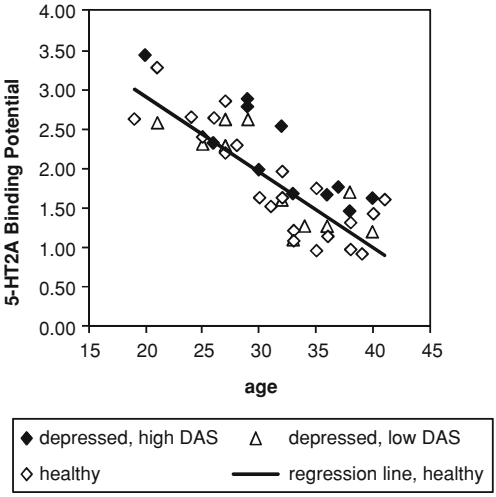

Fig. 4 5-HT_{2A} Binding Potential is Greater During Major Depressive Episodes (MDE) With Highly Abnormal Dysfunctional Attitudes. (5-HT_{2A} receptor binding potential in averaged bilateral middle frontal gyrus (Brodmann's area 9) is plotted against age to show the relationship between depressed and healthy subjects. The 22 depressed patients were divided into high and low dysfunctional attitudes scale (DAS) groups depending upon whether their DAS scores were above or below the median DAS score for the MDE group. This median score was 166. MDE subjects with high DAS scores had significantly higher 5-HT_{2A} receptor binding potential as compared to healthy subjects (ANCOVA (age covariate), diagnosis, $F_{1,19}$=11, p=0.003). (Age was an expected covariate in the model which was designed to identify a disease effect influencing 5-HT_{2A} receptor availability.))

and Mann 1983; Stockmeier 2003; Stockmeier et al. 1997; Turecki et al. 1999; Yates et al. 1990). At the time the studies reported the abnormality as alterations in serotonin$_2$ receptor binding, but it is generally accepted that these studies investigated serotonin$_{2A}$ receptors given that ligand binding to 5-HT_{2C} receptors in cortex is extremely low (Hoyer et al. 1986; Marazziti et al. 1999) and mRNA of 5-HT_{2B} receptors is extremely low in cortex (Schmuck et al. 1994). Although these findings occurred in studies in which the diagnosis of the suicide victim was unrestricted, these findings were more consistent in the subsample of studies of suicide victims who had major depressive disorder and were medication free (Hrdina and Vu 1993; Yates et al. 1990).

The investigations correlating severity of dysfunctional attitudes with greater 5-HT_{2A} BP_{ND} (Meyer et al. 2003; Bhagwagar et al. 2006) explains at a diagnostic and symptom specific level what clinical phenomenon was studied in these postmortem studies: Fifty percent of suicide victims have major depressive disorder (Barraclough et al. 1974; Robins et al. 1959). The dysfunctional attitudes scale is highly correlated with hopelessness measured with the Beck Hopelessness Scale (Bouvard et al. 1992; Cannon et al. 1999; DeRubeis et al. 1990; Norman et al. 1988). Given that hopelessness is a risk factor for suicide (Beck et al. 1985; Beck et al. 1989), it is likely that investigations of suicide victims reporting

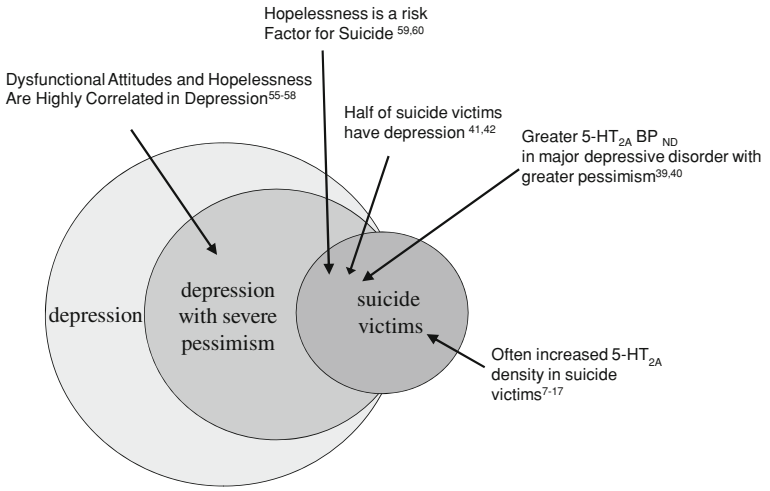

Fig. 5 Elevated prefrontal cortex 5-HT_{2A} density in suicide mainly reflects sampling from major depressive disorder with severe pessimism

increased 5-HT_{2A} BP_{ND} sampled depressed subjects with greater severity of pessimism. See Fig. 5 which represents the relationship of sampling studies for major depressive disorder, dysfunctional attitudes and suicide. Interestingly, while these findings are consistent with postmortem study in suicide victims, they are also consistent with a model of heterogeneous extracellular serotonin loss in prefrontal cortex in MDD such that extracellular serotonin is lowest in major depressive episodes with more severe pessimism.

3.2 5-HTT Imaging and Pessimism

3.2.1 5-HTT Radioligands

In 2000, the first high quality radiotracer for measuring indices of serotonin transporter binding occurred with the development of [^{11}C] DASB. The two previous radiotracers applied for in vivo imaging had significant limitations: 2-beta-carbomethoxy-3-beta-(4-iodophenyl)-tropane (β-CIT) single photon emission tomography (SPECT), the first technique developed had a specific binding signal that could be detected in the midbrain (Brucke et al. 1993; Innis et al. 1993; Kuikka et al. 1993), but it has almost equal affinity for the dopamine transporter as compared to the serotonin transporter (Carroll et al. 1995; Laruelle et al. 1994). Since there is high dopamine transporter density in the substantia nigra (Ciliax et al. 1999), the relative contributions of specific binding to dopamine and serotonin transporters cannot be differentiated in midbrain and it was the midbrain for which this radiotracer technique was applied as an index of serotonin transporter binding. The second applied

radiotracer, [^{11}C](+)McN5652, had better selectivity, but also had a low ratio of specific binding relative to free and non-specific binding. This disadvantage, in combination with modest reversibility makes valid, reliable quantitation difficult in regions other than the thalamus, and impossible in human cortex (Buck et al. 2000; Ikoma et al. 2002; Kent et al. 2002; Parsey et al. 2000). Thus, the radiotracer [^{11}C] (DASB, 3-amino-4-(2-dimethylaminomethyl phenylsulfanyl)-benzonitrile) represented a major advance due to its high selectivity, reversibility, greater specific binding relative to free and non-specific binding and reliability (Ginovart et al. 2001; Houle et al. 2000; Ichise et al. 2003; Meyer et al. 2001b, 2004a, b; Praschak-Rieder et al. 2005; Wilson et al. 2000, 2002).

3.2.2 Interpretations of 5-HTT Binding Measurement

Measurement of serotonin transporter binding can be a useful index for several different models of disease that may affect extracellular serotonin levels. There are at least four such models may be considered in relationship to how serotonin transporter binding may be abnormal in a disease that lowers extracellular brain serotonin (Meyer 2007). These are referred to subsequently as models one through four. Abnormalities in serotonin transporter binding during major depressive episodes may be discussed in the context of these models.

Model one is a lesion model that reduces monoamine releasing neurons. In a lesion model, lowered 5-HTT binding measures occur. Model two is a secondary change in serotonin transporter binding as a sequelae to serotonin lowering via a different process. Model two is unlikely to be relevant for serotonin transporter binding. Acute reductions in serotonin have repeatedly shown reductions in 5-HTT mRNA (Linnet et al. 1995; Xiao et al. 1999; Yu et al. 1995). However, long-term reductions or elevations in serotonin typically show no effect upon regional 5-HTT density (Benmansour et al. 1999; Dewar et al. 1992; Graham et al. 1987). Model three is increased clearance of extracellular monoamine via greater monoamine transporter density. In model three, greater available serotonin transporter binding leads to greater clearance of monoamines from extracellular locations.

Model four is endogenous displacement and endogenous displacement is the property of a few radioligands to express different binding after short-term manipulations of their endogenous neurotransmitter, such that greater binding occurs during depletion of endogenous neurotransmitter and reduced binding occurs during elevations of endogenous neurotransmitter. For [^{11}C] DASB, endogenous displacement may occur with large magnitude changes in extracellular 5-HT, but this is unlikely to occur with extracellular 5-HT changes that are physiologically tolerable for humans (Meyer 2007). For other PET radiotracers such as [^{11}C]HOMADAM, [^{11}C] MADAM, [^{11}C] (+) McN5652, or SPECT radiotracers [^{123}I]-B-CIT SPECT or [^{123}I] ADAM SPECT, it is unknown whether endogenous levels of serotonin influence binding levels. This fourth model is unlikely to apply to PET imaging studies with [^{11}C] DASB in humans, but it is unclear as to whether this model applies to other serotonin transporter radiotracers since the question has not been tested.

3.2.3 Dysfunctional Attitudes During Major Depressive Episodes and 5-HTT Binding

Dysfunctional attitudes, an index of pessimism, are elevated during major depressive disorder, and, as noted above, represent important symptoms because they generates sad mood and are strongly related to suicide. Hopelessness (Beck et al. 1985, 1989) and difficulty seeing positive reasons for living (Malone et al. 2000) are also significant risk factors for suicide and it has been demonstrated in four separate samples of subjects with major depressive episodes that greater hopelessness is highly positively correlated with greater severity of dysfunctional attitudes as measured with the dysfunctional attitudes scale (Bouvard et al. 1992; Cannon et al. 1999; DeRubeis et al. 1990; Norman et al. 1988).

In the two postmortem investigations of 5-HTT density in subjects with recent symptoms of depressive episodes no changes in 5-HTT density in the dorsal raphe or the locus coeruleus were found (Bligh-Glover et al. 2000; Klimek et al. 2003). Other postmortem investigations of 5-HTT density sampled subjects with a history of a depressive episode and these investigations usually studied the prefrontal cortex and/or dorsal raphe nucleus. Findings ranged from decreased 5-HTT density (Arango et al. 2001, Austin et al. 2002; Crow et al. 1984; Mann et al. 2000; Perry et al. 1983) to no difference in 5-HTT density (Hendricksen et al. 2004; Hrdina et al. 1990; Lawrence et al. 1990; Leake et al. 1991; Little et al. 1997). In several of these studies, subjects were medication free (Hrdina et al. 1990; Lawrence et al. 1990; Mann et al. 2000) and for many of these investigations, average postmortem delay was less than 1 day (Austin et al. 2002; Bligh-Glover et al. 2000; Klimek et al. 2003; Little et al. 1997; Mann et al. 2000; Perry et al. 1983). Further detail may be found in the review of Stockmeier (2003). Other sampling issues that influence postmortem investigations are inclusion of subjects with bipolar disorder and lack of differentiation between early versus late onset MDD. None of the postmortem studies investigated the relationship between 5-HTT binding and hopelessness or pessimism.

The first investigation of [^{11}C]DASB PET imaging of major depressive disorder examined the relationship of 5-HTT BP_{ND} to severity of dysfunctional attitudes and presence of a major depressive episode. Meyer et al., sampled 20 subjects with major depressive episodes (from early onset major depressive disorder) and 20 healthy controls (Meyer et al. 2004a). Subjects were medication free for at least 3 months, had no other comorbid axis I illnesses, were nonsmoking, and had early onset major depressive disorder. There was no difference in 5-HTT BP_{ND} in either cortical or subcortical regions (including medial prefrontal cortex, dorsolateral prefrontal cortex and anterior cingulate cortex) between the group with major depressive episodes and healthy controls. However, subjects with severely pessimistic dysfunctional attitudes who were in the midst of major depressive episodes had significantly higher 5-HTT BP_{ND}, compared to healthy in brain regions sampling serotonin nerve terminals (dorsolateral and medial prefrontal cortex, anterior cingulated cortex, thalamus, bilateral caudate and bilateral putamen). On average, 5-HTT BP_{ND} was 21 % greater in these regions in subjects who were in

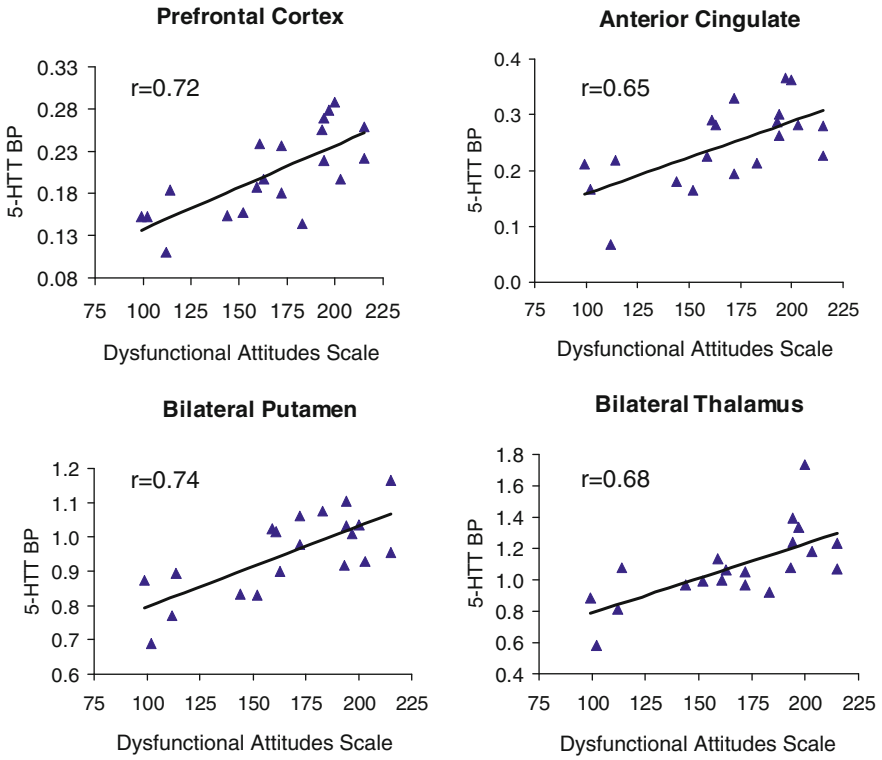

Fig. 6 Correlations between dysfunctional attitudes (DAS) and serotonin transporter binding potential (5-HTT BP) in some of the larger regions in depressed subjects. Highly significant correlations were found: prefrontal cortex (P = 0.0004), anterior cingulate (P = 0.002), bilateral putamen (P = 0.0002), bilateral thalamus (P = 0.001). Reprinted from the Archives of General Psychiatry

the midst of major depressive episodes with severely pessimistic dysfunctional attitudes. Moreover, within the major depressive episode group, greater 5-HTT BP_{ND} was highly correlated with more negativistic dysfunctional attitudes in the same brain regions (see Fig. 6). The interpretation was that given serotonin transporters have an important role in influencing extracellular serotonin, greater regional 5-HTT levels provide greater vulnerability to low extracellular 5-HT and symptoms of extremely negativistic dysfunctional attitudes. This interpretation, in subjects with high levels of pessimism during MDE, corresponds to the third model discussed earlier under "Interpretations of 5-HTT Binding Measurement".

Neuroimaging investigations, sampling subjects with early onset MDD who are medication free for greater than 2 months, are non-smoking and do not have comorbid axis I disorders, and also apply better quality radiotracer technology, tend to find either no change in regional 5-HTT binding or an increase in regional 5-HTT binding (Cannon et al. 2007; Herold et al. 2006; Ichimiya et al. 2002; Meyer et al. 2004a). Investigations which include sampling of subjects with late onset MDD,

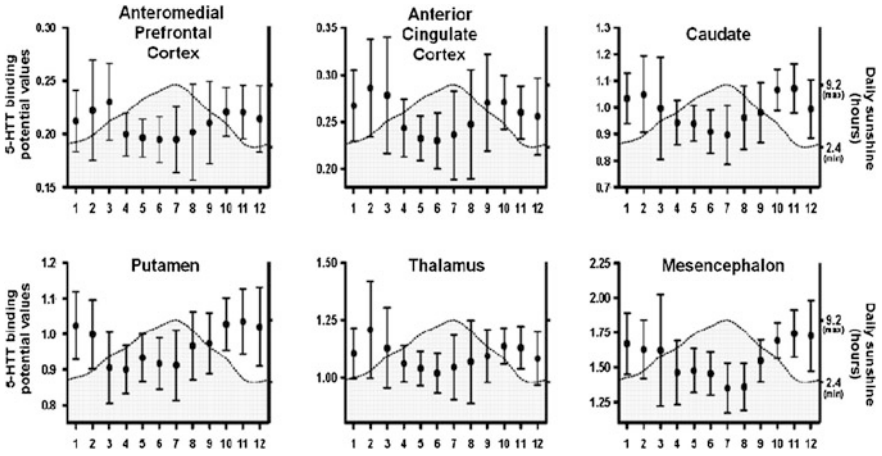

Fig. 7 Regional 5-HTT BP_{ND} versus month (n=88 healthy subjects). Reciprocal peaks and troughs of brain serotonin transporter binding and duration of sunshine in 88 healthy study participants. Serotonin transporter binding potential values were measured in six brain regions. Circles represent bimonthly moving average means. Error bars represent 95 per cent confidence intervals of the mean. The shaded areas represent the average duration of sunshine in Toronto, Ontario, Canada. Regional 5-HTT BP_{ND} was significantly greater in spring/summer than fall/winter by 10 to 16%, $p<0.02$ for each region. Differences in peak to trough ranged from 22 to 42%. Reprinted from Meyer et al., Archives of General Psychiatry 65(9):1072–1078

comorbid axis I psychiatric disorders, recent antidepressant use, current cigarette smoking and do not apply a selective radiotracer are more likely to report a reduction in regional 5-HTT binding (Joensuu et al. 2007; Malison et al. 1998; Newberg et al. 2005; Parsey et al. 2006a; Selvaraj et al. 2009). Only the first study of [^{11}C] DASB PET concurrently investigated a measure of pessimism or hopelessness.

3.2.4 Serotonin Transporter Binding and Seasonal Behaviour

Seasonal affective disorder is an important problem for countries with regions located at greater extremes of latitude. Rates of SAD typically range from 1 to 6 % in regions of 40′ latitude or greater (Magnusson 2000). Furthermore, at these latitudes, 25 % of healthy individuals experience lower mood, less energy, greater appetite and increased sleep in the winter (Kasper et al. 1989; Rosen et al. 1990).

There is significant evidence for seasonal variations in markers of serotonin physiology. In postmortem study of serotonin concentrations, Carlsson et al. reported a seasonal variation of serotonin levels in human hypothalamus with lower levels in late winter and higher levels in late summer (Carlsson et al. 1980). More recently, Lambert et al. found seasonal fluctuations in whole brain serotonin turnover in humans (Lambert et al. 2002). In rodents, reduced light exposure is associated with greater 5-HTT density (Rovescalli et al. 1989), lower 5-HT release (Blier et al. 1989) and greater 5-HT clearance (Rovescalli et al. 1989) in the

hypothalamus and suprachiasmatic nucleus. It is possible that these findings were region specific or that the effect of light is more detectable in these regions of high 5-HT concentration and density.

While seasonal variation in pessimism has not been studied, the relationship of 5-HTT BP_{ND} to season has been subject to a number of interesting investigations. In a study of 5-HTT BP_{ND} with [^{11}C] DASB PET in 88 healthy, non-smoking humans in Toronto, Canada, greater 5-HTT binding occurred in the fall/winter as compared to spring/summer in a number of affect modulating brain regions (Praschak-Rieder et al. 2008) (see Fig. 7). Another centre in Copenhagen, located at a latitude more north than Toronto replicated the effect of season in a sample of 54 subjects using [^{11}C] DASB PET (Kalbitzer et al. 2009, seasonal changes in brain serotonin transporter, personal communication). In a combined sample of 49 healthy subjects and 49 depressed subjects, Ruhe et al. reported a similar relationship between midbrain binding and season (Ruhe et al. 2009) (although [^{123}I]B-CIT SPECT is not very selective for 5-HTT). Buchert et al. reported the same seasonal finding in the midbrain in a sample of 39 subjects using [^{11}C] McN5652 PET but not in the thalamus (Buchert et al. 2006). Although the Buchert study reported a positive result in only one of the two regions assayed, the sensitivity of this study to detect seasonal change was more modest: the sample is smaller than the other studies, and [^{11}C] McN5652 is a less sensitive technique than [^{11}C] DASB (Meyer 2007, 2008; Kent et al. 2002; Meyer et al. 2001b, 2004b). There are two studies in the literature that do not report greater 5-HTT binding in winter and both have a small sample size ($n = 12$ or less) (Koskela et al. 2008; Neumeister et al. 2000). To date, most studies of large sample size and reasonably northern latitude report greater 5-HTT BP_{ND} in most brain regions in the fall/winter as compared to spring/summer.

3.3 5-HT_{1A} Receptor Binding and Anxiety

Most [^{11}C] WAY-100635 PET studies report lower 5-HT_{1A} BP_{ND} in subregions of prefrontal cortex (dorsolateral, ventrolateral, orbitofrontal), anterior cingulate cortex, temporal cortex and raphe during major depressive episodes and continuance of this reduction during remission (Bhagwagar et al. 2004; Drevets et al. 1999; Sargent et al. 2000). There is one study with a different result and it may be that the selection of white matter as a reference region, and/or sampling characteristics may account for the difference (Parsey et al. 2006b). A potential problem with applying white matter as a reference tissue is that in contrast to using grey matter in cerebellar cortex, the properties of white matter are more likely to be different from grey matter, and the modelling method requires the assumption that the free and non-specific binding in the reference tissue is similar to grey matter tissue. Hence, a grey matter region with low specific binding is preferable as a reference tissue such as the cerebellar cortex excluding the vermis.

There is reason to consider that finding in MDD may actually be more strongly associated with anxiety, which often occurs during major depressive episodes or presence of comorbid anxiety disorders, which also frequently occur with MDD since reduced 5-HT_{1A} binding also occurs in affect modulating regions also occurs in anxiety disorders. In a [^{18}F]trans-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-pyridyl) cyclohexanecarboxamide ([^{18}F]-FCWAY) study of panic disorder (with comorbid MDD in almost half the subject sample), significant reductions in 5-HT_{1A} binding in anterior cingulate, posterior cingulate and raphe regions were reported (Neumeister et al. 2004a). (Quantitation with this radiotracer is valid for subcortical regions but not cortical regions due to bone uptake of radiotracer metabolite.) A second study applying [^{11}C] WAY100635 reported similar findings with the greatest magnitude being in orbitofrontal cortex, temporal cortex and midbrain (Nash et al. 2008). In social anxiety disorder, reduced 5-HT_{1A} binding occurs in most brain regions (insula, anterior cingulate cortex, medial orbitofrontal cortex, amygdala and midbrain) (Lanzenberger et al. 2007). Since the neuroimaging studies of 5-HT_{1A} binding in MDD did not exclude comorbid anxiety disorders, one interpretation of the reduced 5-HT_{1A} binding in the brain regions assayed in MDD, particularly in orbitofrontal cortex, anterior cingulate cortex and midbrain, is that it reflects comorbid anxiety disorders. MDD with anxiety is often treatment resistant, and this interpretation is appealing because there could be an opportunity to target pathologies related to this abnormality in this treatment resistant subgroup (Trivedi et al. 2006).

A limitation of this interpretation is that a postmortem study with subjects who mainly did not have comorbid anxiety disorders reported decreased 5-HT_{1A} antagonist binding in orbitofrontal cortex (Stockmeier et al. 2009) and another explanation could be that abnormally low 5-HT_{1A} density in prefrontal and cingulate cortex is associated with both MDD and anxiety disorders. Future work should investigate the cellular mechanism, and identify the clinical subgroup of MDD with this finding so as to optimise therapeutics. One explanation is that lower 5-HT_{1A} receptor density reflects decreased 5-HT_{1A} receptors on GABA interneurons or the segments of pyramidal cell axons proximal to extensions from GABA containing chandelier interneurons (Stockmeier et al. 2009).

4 D_2, DAT and Motor Slowing

4.1 Dorsal Striatal [^{11}C]Raclopride Binding and Motor Retardation in Major Depressive Disorder

Among the symptoms of MDEs, motor retardation and anhedonia both reflect functions modulated by dopamine release in the dorsal putamen and nucleus accumbens respectively. The second symptom, anhedonia, is more difficult to investigate with neuroimaging markers of dopamine: The nucleus accumbens is a

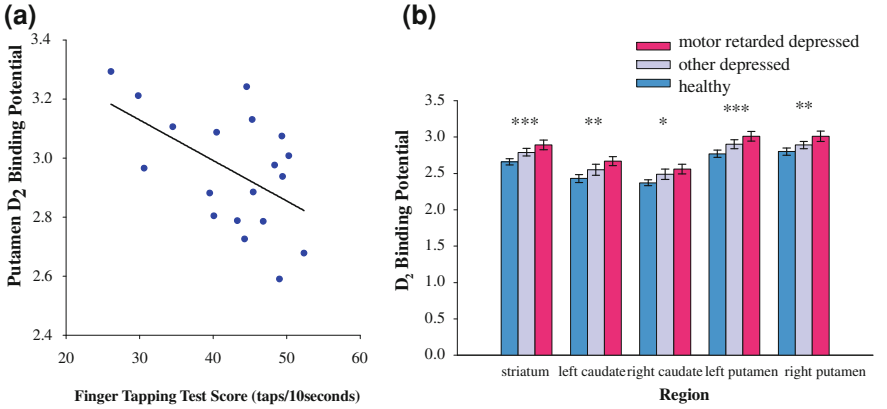

Fig. 8 (**a**) Correlation between bilateral putamen D_2 receptor binding potential and motor speed in depressed (n=19) subjects (The correlation was significant (r = -0.53, p = 0.02). In order to reduce variance related to age and gender, individual putamen D_2 BP values were normalized to age 30 using the slope of the linear decline in D_2 BP with age. Motor speed was measured with the finger tapping test. Individual finger tapping scores were normalized similarly to a 30 year old male (Meyer et al. 2006a, b). (**b**) Striatal D_2 Receptor Binding Potential in Motor Retarded Depressed (n=10), Other Depressed (n=11) and Healthy Subjects (n=21) (Striatal D_2 Receptor Binding Potential in Motor Retarded Depressed (n=10), Other Depressed (n=11) and Healthy Subjects (n=21) (D2 binding potential values were normalized to a 30-year-old subject using the slope of the age-related decline. Differences between the healthy group and the depressed subjects with motor retardation assessed by means of independent sample t tests. *$p \leq 0.05$ **$p \leq 0.01$ ***$p \leq 0.005$)

smaller structure. Anhedonia is difficult to measure during major depressive episodes since it can be biased by negativistic perspective if the measure involves self report or motor speed if the measure involves movement. However, given recent advances in the development of neuroimaging markers for D_3 receptors for the ventral striatum, and ongoing development of quantitation of hedonic measures in depression, it is likely that future investigations will focus upon this direction (Willeit et al. 2008). The first symptom, motor retardation, is straightforward to investigate with quantitative measures because dorsal putamen is large, motor retardation can be measured with well validated motor tests such as the finger tapping test, and [^{11}C] raclopride has a strong specific binding signal in dorsal putamen. [^{11}C] raclopride is a widely available PET radiotracer selective for D_2 type receptors whose specific binding changes inversely relative to changes in neurotransmitter levels (Laruelle 2000).

In addition to the straightforward ability to quantify D_2 BP_{ND} in dorsal striatum, there were other reasons to investigate this biomarker in relation to motor retardation. One is that greater D_2 BP_{ND} and reduced dopamine levels occur in dorsal striatum in Parkinson's disease and other similar diseases that involve reduced movement speed (Kim et al. 2002; Kish et al. 1988). The second is that D_2 BP_{ND} found with [^{11}C]raclopride PET, is inversely proportional to extracellular dopamine levels in animal and human paradigms that manipulate dopamine levels (Laruelle 2000). The third reason is that decreased cerebrospinal fluid levels of the

dopamine metabolite homovanillic acid is often reported during MDE with motor retardation, suggesting that some regions of the brain have lower levels of dopamine when motor retardation is present during major depressive episodes (Korf and Praag 1971; Post et al. 1973; Praag et al. 1975).

Unfortunately, early imaging studies of dopamine receptors did not sample depressed subjects who were medication free and non-smoking or addressing the confounding effect of age (Meyer 2008). Since D_2 BP_{ND} declines with age and motor retardation increases with age, to assess this relationship in a manner that addressed the age bias, one must correct for the effect of age upon each variable prior to investigating the relationship between the two. There is only one study that meets all of these criteria, and there is no other study meeting two of these three criteria (Meyer 2008). The main findings of the one, unbiased study, of striatal D_2 BP_{ND} and motor retardation were that the caudate and putamen D_2 BP_{ND} were elevated in the depressed group as compared to the healthy group, and that greater putamen D_2 BP_{ND} was significantly correlated with more severe motor retardation in the depressed group (Meyer et al. 2006b) (see Fig. 8). The findings support a specific, neuromodulatory role for striatal dopamine loss during MDE, particularly when motor retardation is present.

4.2 Striatal DAT Binding and Motor Retardation During Major Depressive Episodes

With regard to dopamine transporter (DAT) imaging in MDD, studies sampling medication free subjects typically report lower striatal DAT BP_{ND} (Meyer et al. 2001a; Neumeister et al. 2001; Sarchiapone et al. 2006), whereas studies sampling subjects with recent antidepressant treatment sometimes report higher striatal DAT binding (Brunswick et al. 2003). Most studies address the age-related decline in DAT and some address the confound of cigarette smoking. Mechanisms to explain reduced striatal DAT binding include lesions to dopamine releasing neurons or a downregulation model (in response to another monoamine lowering process). In contrast to the serotonin transporter, dopamine transporters in the striatum downregulate when subacute to chronic dopamine depletion occurs (Gordon et al. 1996; Han et al. 1999; Ikawa et al. 1993; Kilbourn et al. 1992).

The downregulation model may explain reduced striatal DAT binding during MDD since greater MAO-A levels occur in striatum in major depressive episodes and MAO-A metabolises dopamine (Meyer et al. 2006a, 2009). In addition, greater striatal D_2 BP_{ND} was found during major depressive episodes with [^{11}C]raclopride PET and this index is increased when extracellular dopamine is reduced (Laruelle 2000).

Also, the correlation between lower dorsal putamen DAT BP_{ND} values and less impaired performance on the finger tapping test has a particular interpretation (Meyer et al. 2001a). The finger tapping test is a measure of motor slowing in MDD (Meyer et al. 2001a, 2006b). Slower performance on the finger tapping test is

correlated with greater putamen D_2 BP_{ND} during MDE and greater D_2 BP_{ND} from [^{11}C] raclopride occurs when extracellular dopamine is lower (Laruelle 2000). The data can be interpreted as follows: Major depressive episodes without motor retardation are associated with lower DAT BP_{ND} and demonstrate a compensatory protective mechanism (Meyer et al. 2001a). Downregulation of DAT occurs when dopamine is chronically low in striatum (Gordon et al. 1996; Han et al. 1999; Ikawa et al. 1993; Kilbourn et al. 1992), but reduced DAT levels decrease clearance of extracellular dopamine. Compared with the healthy state, the compensated state has only mildly reduced extracellular striatal dopamine concentrations with downregulated DAT. This is the process whereby dorsal striatal DAT BP_{ND} is decreased protects against motor slowing.

5 Behavioural Correlates of With Abnormalities in Glutatmate Regulation

Magnetic resonance spectroscopy (MRS) can measure 'Glx' in brain tissue, an index mainly composed of glutamate (intracellular and extracellular), and glutamine. Exposure to elevated glutamate levels has been proposed as a mechanism that leads to sad mood because treatment resistant MDD subjects often experience a rapid, short term, mood elevation after single dose ketamine, a NMDA receptor antagonist and some subtypes of MDE have a response to lamotrigine, a medication that can reduce glutamate release (Barbee and Jamhour 2002; Barbee et al. 2011; Zarate et al. 2006). Also, elevations in extracellular glutamate have been proposed as being relevant to mood symptoms because reductions in glia are reported in orbitofrontal, dorsolateral prefrontal and anterior cingulate cortex in MDD and glia clear glutamate via excitatory amino acid transporters (Rajkowska and Miguel-Hidalgo 2007).

There are several studies applying proton MRS to measure Glx, in reasonably large samples of MDD with region specific results. For example, greater Glx levels were reported in the occipital cortex, a reduction was reported in the medial prefrontal cortex and no change was reported in the pregenual cingulate cortex (Hasler et al. 2007; Sanacora et al. 2004; Walter et al. 2009). A reasonable explanation for the anatomical variation is that glutamate levels are generally elevated in the brain during MDD, and that regions with reduced glial cell density (Rajkowska and Miguel-Hidalgo 2007) have reduced Glx because the intracellular contribution of Glx signal are lower. Some level of homogenous abnormality in brain glutamate regulation during MDD is suggested by a recent [^{11}C]ABP688 study reporting reduced prefrontal cortex, cingulate cortex, insula, thalamus and hippocampus mGlu5 receptor binding in conjunction with a postmortem study of reduced mGlu5 density in prefrontal cortex (Deschwanden et al. 2011). The investigation of pregenual cingulate cortex did detect, in highly anhedonic depressed subjects, decreased glutamine, a metabolic product of glutamate (Walter et al. 2009) and the

investigation reporting greater glutamate in the occipital cortex found the greatest levels in melancholia (Hasler et al. 2007; Sanacora et al. 2004; Walter et al. 2009). Ideally, future studies should aim to sample the regions previously investigated concurrently so as to optimally address the regional specificity of findings, and preferentially sample melancholic and anhedonic subjects so as to replicate the findings by Sanacora et al. (2004) and Walter et al.(2009). While there is evidence for disturbances in glutamate levels during major depressive episodes, the mechanism of the relationship to specific mood symptoms requires further study.

6 Conclusions

While neuroimaging is limited by the range in biomarkers available, its ability for in vivo measurement is bridging markers of neurochemistry and neuroplasticity to pathophysiological mechanism of symptom onset for major depressive disorder. For example, indices of greater monoamine oxidase A (MAO-A) level, particularly in the prefrontal and anterior cingulate cortex, are associated with depressed mood states, and high-risk states for onset of major depressive episodes. MAO-A metabolises monoamines, and greater metabolism of monoamines occurs when MAO-A is elevated in brain. Hence, greater levels of MAO-A may be viewed as a key monoamine lowering process during major depressive episodes.

Evidence to date suggests that ongoing deficiency of specific monoamines in specific regions is implicated in symptoms of disease. Lower extracellular serotonin is associated with greater pessimism in humans and chronic serotonin deficiency is associated with upregulation of 5-HT_{2A} (serotonin$_{2A}$) receptors in cortex. During major depressive episodes, when pessimism is more severe, greater 5-HT_{2A} binding occurs in prefrontal and anterior cingulate cortex. These results argue for a mechanism of lowering extracellular serotonin in the prefrontal and anterior cingulate cortex, consequent to elevated MAO-A level. The relationship between elevated 5-HTT binding greater pessimism during major depressive episodes suggests that greater 5-HTT density in the context of elevated MAO-A level further contributes to serotonin deficiency in these brain regions (see Fig. 9). A similar mechanism may explain the association between neuroimaging indices of greater dorsal striatal D_2 density, DAT density and symptoms of motor retardation: Greater MAO-A level and relatively greater DAT density lower extracellular dopamine in the dorsal striatum, leading to motor retardation (also see Fig. 9).

Specific mechanisms underlying other neuroimaging abnormalities continue to be investigated. Indices of greater 5-HT_{1A} density, particularly in the cingulate cortex, have been associated with major depressive disorder, and well as anxiety disorders, suggesting that this abnormality is mechanistically related to presence of anxiety symptoms. At this point, abnormalities in glutamate level have been most strongly associated with presence of major depressive episodes, with greater levels in occipital cortex, and reduced levels in prefrontal cortex. Future neurochemical imaging investigations will ultimately focus upon detecting the mechanisms that

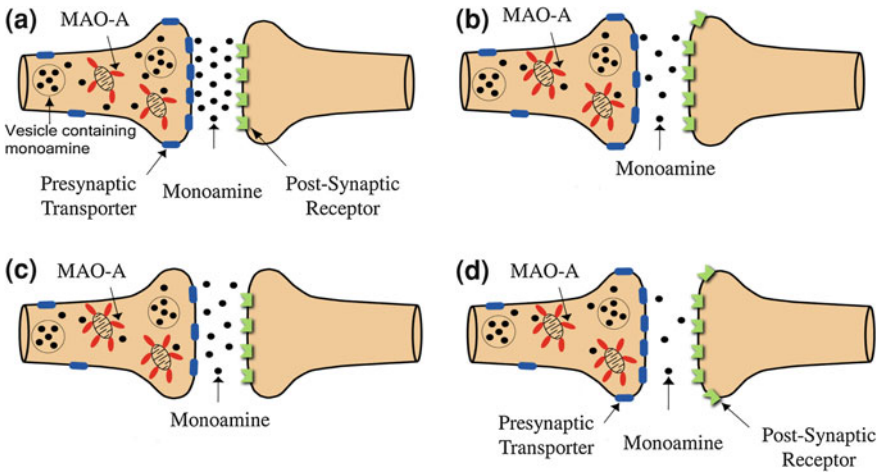

Fig. 9 Modern Model of Excessive Extracellular Monoamine Loss During Major Depressive Disorder (**a**) Monoamine release in a synapse in health. (**b**) During a major depressive episode, monoamine oxidase A (MAO-A) density is elevated resulting in greater metabolism of monoamines. Outcomes range from (**c**) to (**d**). (**c**) If the monoaminge transporter density is low during a major depressive episode, the effect of elevated MAO-A upon reducing extracellular monoamine is attenuated resulting in a moderate loss of monoamine, eventually resulting in a moderate rise in symptoms. (**d**) If the monoamine transporter density is not low during a major depressive episode, then there is no protection against the effect of elevated MAO-A. The extracellular concentration of the monoamine is severely reduced and rise in symptom s is severe. This model applies to regions whose functions are affected by changes in monoamine levels. Studies of transporter binding related binding to function (such as motor retardation to striatal DAT binding, and pessmism to prefrontal/anterior cingulate cortex 5-HTT binding. MAO-A in cell types not proximal to the release of the individual monoamine may play a role in its metabolism (for example MAO-A in norepinephrine releasing neurons, glia, and astrocytes may also play a role in the metabolism of serotonin)

predispose towards onset of MDE so as to create new biologically informed methods of prevention, and superior, more symptom targeted treatments based upon symptom specific underlying pathology.

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