



Review

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Imaging the serotonin 1A receptor using [¹¹C]WAY100635 in healthy controls and major depression

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As a neurotransmitter, serotonin (5-HT) is widely used throughout the brain and known to play a role in many processes including emotion and brain development. Of the 15 subtypes of 5-HT receptors, the 1A receptor (5-HT_{1A}) has been implicated in depression and suicide. Using the [carbonyl-¹¹C]WAY100635 ([¹¹C]WAY) ligand and positron emission tomography, we have studied the 5-HT_{1A} receptor, first in a group of healthy controls, then in two separate groups of subjects with major depressive disorder (MDD) (antidepressant exposed and not recently medicated), and, lastly, in a group of subjects remitted from MDD. All MDD subjects were medication-free at the time of scan. We found higher 5-HT_{1A} binding potential (BP_F) in MDD subjects not recently exposed to an antidepressant compared with controls and recently medicated MDD subjects; and higher BP_F in subjects with the C(-1019)G promoter polymorphism. We replicated these findings in a novel cohort and reconciled our discrepant findings with other groups using alternate quantification techniques. We also reported higher BP_F in subjects remitted from a major depressive episode than in controls. From this work, we proposed a temporal model in which 5-HT_{1A} BP_F may be a trait abnormality of MDD. To further explore the genetic components of MDD and utility of 5-HT_{1A} imaging as a potential tool for biomarker or treatment response prediction, these findings should be replicated in a larger cohort using the [¹¹C]CUMI-101 agonist tracer.

1. Introduction

Serotonin is one of the most widely recognized neurotransmitters. To date, 15 subtypes of serotonin receptors have been identified in the brain and throughout the body [1]. The serotonergic system has been implicated in various psychiatric disorders and conditions such as anxiety [2], chronic stress [3], schizophrenia, major depressive disorder (MDD) and suicide [4]. Major depression is particularly pervasive in that estimates approximate a 6.7 per cent prevalence rate in adults over a twelve month period [5] and 13 per cent prevalence over the lifetime [6]. Moreover, MDD is associated with an increased risk in suicide and overall poorer health. Economic estimates suggest the burden of MDD is greater than 10 billion dollars owing to disability, loss of productivity and treatment [7–9], whereas projections indicate MDD will become the second greatest contributor to disability across all age groups by the year 2020 [10].

There is great utility in the quantification of neuroreceptors in understanding and possibly treating major depressive disorder. Characterizing the function or dysfunction of specific receptors in MDD will lead to better understanding of the disorder and plausible utility of these receptors as biomarkers, which could further improve treatment paradigms or help in predicting treatment response. Positron emission tomography (PET) is one modality through which serotonin receptors can be imaged in various disorders, including MDD.

Animal studies [11,12], antidepressant treatment response [13] and post-mortem [14] studies have implicated the serotonin 1A receptor (5-HT_{1A}) in

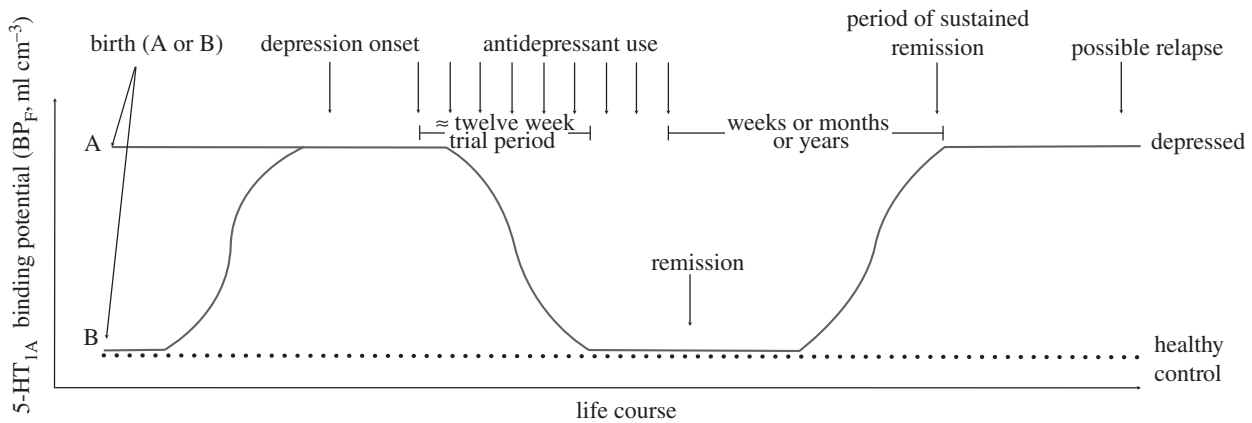


Figure 1. Temporal model of serotonin 1A receptor binding potential over the lifetime of subjects with major depression compared with controls. Subjects may be born with a preexisting vulnerability towards major depression (position A) or not (position B).

MDD, which can be imaged using the [carbonyl- ^{11}C]-WAY100635 (^{11}C WAY) ligand. Pike *et al.* [15] previously described the selectivity and sensitivity of ^{11}C -WAY as a PET ligand, and the characteristics which make this ligand more amenable to quantification and modelling than its predecessors [15]. Using the ^{11}C WAY ligand, we have carefully characterized its modelling and binding in healthy controls, taken the ligand into clinical populations, determined human dosimetry and replicated our initial findings in a second cohort. This work has led us to develop a temporal model in which we purport alterations in 5-HT $_{1A}$ binding may be a trait abnormality in subjects with MDD compared with controls (figure 1; [16]).

2. Quantifying and characterizing ^{11}C WAY binding

In order to develop this model, it was necessary to quantify PET imaging data across subjects. In this quantification, the primary outcome measures of interest are binding potentials: $\text{BP}_F((V_T - V_{ND})/f_P)$, $\text{BP}_F(V_T - V_{ND})$ and $\text{BP}_{ND}((V_T - V_{ND})/V_{ND})$; where V_T is the total volume of distribution in a region of interest, V_{ND} is the total non-specific binding usually measured in reference tissue, and f_P is the plasma free fraction [17]. While BP_{ND} may be the easiest outcome measure to obtain as it does not require an arterial input function, it does require the most assumptions: namely that there is a reliable reference region that is devoid of specific binding, does not differ between groups and can be fit with a one-tissue compartment (1-TC) model [18]. On the other hand, BP_F requires full arterial sampling, but makes the fewest assumptions and provides the measure closest *in vivo* to B_{\max}/K_D , a measure of receptor density. With some tracers but not all, BP_F obtained through arterial sampling also outperforms BP_{ND} quantified via reference tissue methods [19,20] with regard to reproducibility and bias [21].

As previously mentioned, a good reference region is imperative to performing quantitative PET. Both reference tissue and kinetic analysis methods require an estimate of non-specific binding (V_{ND}) to calculate any of the three outcome measures. With low levels of 5-HT $_{1A}$ receptors, the cerebellum is commonly used as the reference region. Yet, we estimated specific binding (V_T) in the cerebellum to be approximately 48 per cent [22], which *in vitro* data suggest

is concentrated in the cerebellar vermis and grey matter. Therefore, to avoid biasing the V_{ND} estimate, we used and recommend using a region most devoid of receptors, such as cerebellar white matter (CWM), as reference tissue for *in vivo* quantification. As compared with a total cerebellar reference region, CWM is better fit with a 1-TC model and improves reproducibility and identifiability [22]. Hirvonen *et al.* [23] also assert that CWM may be used as an optimal reference region for kinetic analysis of ^{11}C WAY [24].

Choosing appropriate modelling methods and reference regions is imperative to data analysis, as different techniques may effect the interpretation of the results. While reference region methods may be desirable in clinical settings because they do not require an arterial line and, thus, are less physically demanding on the subject, they consistently underestimate ^{11}C WAY binding [18,21]. Similarly, using the total cerebellum as reference region would underestimate binding and possibly obfuscate the direction of any hypothesized group differences, because V_{ND} , which is subtracted from the V_T of the region of interest, contains measurable specific binding. Taken together, these findings suggest that kinetic modelling with an arterial input function and CWM as reference region provides the best quantitative estimates of BP_F when using ^{11}C WAY.

Satisfied with the optimal modelling methods, we proceeded to characterize the ligand in a group of healthy control subjects. Previous studies reported age [25], sex [26,27] and aggression [28,29] dependencies on 5-HT $_{1A}$ estimates, although not all in consistent directions. Consistent with Rabiner *et al.* [30] we did not find an age dependency in our group of healthy controls. However, we did find lower 5-HT $_{1A}$ BP_F in males compared with females, consistent with post-mortem findings [26], but only partially consistent with BP_{ND} findings from Moses-Kolko *et al.* [27]. We also reported an inverse correlation between lifetime aggression and BP_F [31], consistent with pre-clinical data [28,29]. Having identified these covariates in our subject group, future studies using ^{11}C WAY should therefore incorporate both sex and aggression as covariates in the statistical model.

Our primary statistical analyses consist of linear mixed effects models with the subject as the random effect and region, and diagnostic group as fixed effects. Including all regions of interest in the model simultaneously increases the power and accounts for the correlation between regions within a subject, while decreasing the issue of multiple

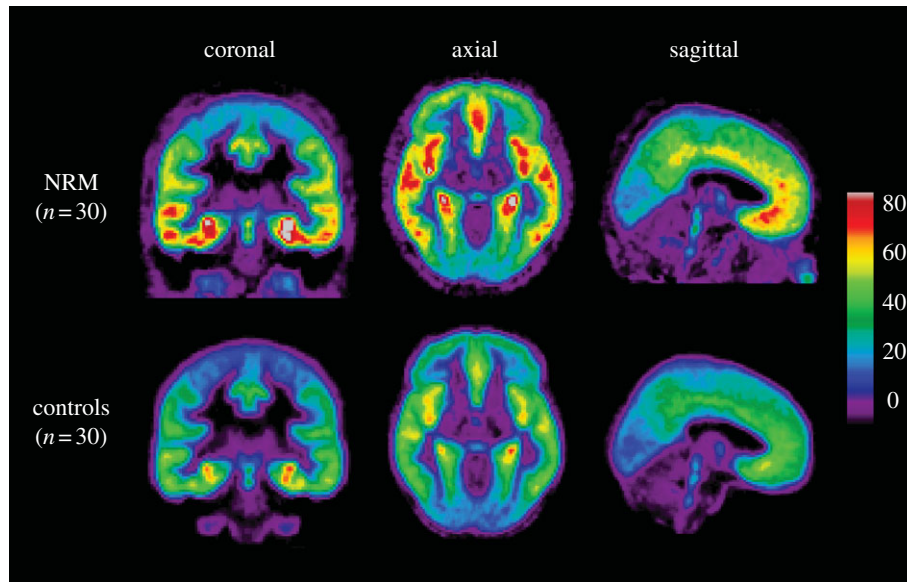


Figure 2. Mean voxel BP_F maps of 5-HT_{1A} [carbonyl-¹¹C]WAY100635 binding. Not recently medicated (NRM) subjects show visibly higher binding throughout the brain than do controls.

comparisons. All analyses including more than one region of interest are done on log-transformed data to reduce variance and alleviate any skewness [32]. Additionally, our observations are weighted with standard errors estimated using a bootstrap algorithm which takes into account errors in the plasma, metabolite and brain data [33]. Once the model is built, individual variables like sex and aggression can be incorporated into the model as covariates when appropriate.

3. [¹¹C]WAY binding in major depression: first cohort, replication and reconciliation

Following previous publications reporting lower 5-HT_{1A} binding in depressed subjects compared with controls [34,35], we hypothesized similar group differences in our cohort. However, using the optimal modelling and reference region methods we previously described, we found higher BP_F in not recently medicated (NRM) subjects in the midst of a depressive episode compared with both currently depressed subjects with prior antidepressant exposure within the past 4 years and healthy controls [36]. The findings remained significant when we included sex and aggression in the model. Also, consistent with Lemonde *et al.* [37], in this same subject group, we found a significant effect of the 5-HT_{1A}C(-1019)G promoter polymorphism in the dorsal raphe region of interest: specifically, BP_F increased with number of G alleles. These findings raised several questions relating to the genetic predisposition of depression, the effect of antidepressant exposure, possible treatment resistance and major depression as a state or trait phenomenon.

Concurrent with the aforementioned study, we questioned the acceptable limits of the radiation dose associated with [¹¹C]WAY. A closer look at the human dosimetry of the WAY ligand revealed that the renal system comprised the critical organs, which is discordant with the extrapolated data from rat studies identifying the liver as the critical organ [38]. From this novel *in vivo* data, we recommended the dose be limited to under 300 MBq in men and 227 MBq in women, and adjusted our studies accordingly.

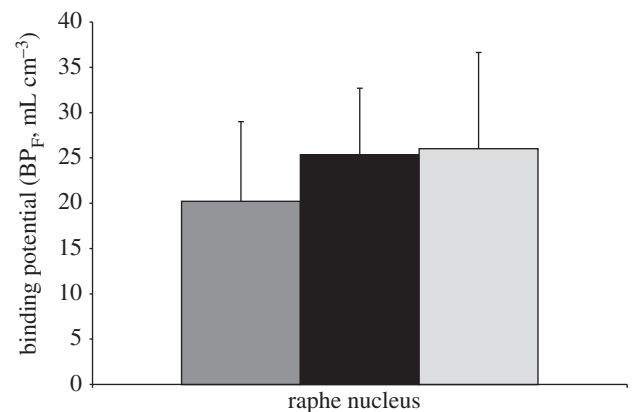


Figure 3. The C(-1019)G 5-HT_{1A} promoter polymorphism in controls and NRM subjects. Binding potential (BP_F) shows a stepwise increase in the raphe nuclei with G allele frequency: CC < CG < GG (d.f. = 1,78; $F = 7.13$; $p = 0.009$). The height of the bars indicates the weighted mean BP_F , while the error bars represent the corresponding equivalent of the standard deviation of each weighted mean. Dark grey bar represents CC ($n = 22$), black bar represents CG ($n = 47$) and light grey bar represents GG ($n = 11$).

With the new limits on injected dose, we replicated our finding of higher BP_F in NRM subjects compared with controls in a novel cohort (figure 2; [32]). The finding remained significant when we combined the two cohorts and included covariates in the model: injected dose, injected mass, aggression and sex. We also replicated the genotype finding in the larger sample (figure 3).

In addition to the replication, within this combined sample we were able to reconcile some of the discrepant findings between our group and others. Similar to Hirvonen *et al.* [23], we found no differences between NRM MDD and controls using BP_{ND} from a reference tissue model. However, using the same model but with cerebellar grey matter (CGM) as reference tissue, we found lower BP_{ND} in the NRM MDD subjects compared with controls. Although this is consistent with some previous reports [34,35,39], it is more likely to be reflective of differences in specific binding

in the reference region, as we also found significantly different V_T in CGM between NRM MDD and controls. To address the issue of specific binding in the reference tissue, we reanalysed pindolol blockade data [40]. We reported changes in CGM but not CWM following pindolol administration, which again demonstrates measurable *in vivo* specific binding in CGM, and further supports the use of CWM as a measure of non-specific binding for the reference region.

4. Future directions and implications

Our finding of higher 5-HT_{1A} in NRM MDD is replicable and also consistent with post-mortem data [26], as well as data from other modalities [29,37,41]. Furthermore, it lends additional support to the hypothesis of higher 5-HT_{1A} in depression and agrees with the purported model underlying selective serotonin reuptake inhibitors (SSRIs) [42,43]. Although it is known that not all patients will respond to SSRIs, it is often the first line of treatment sought and used [44]. Under naturalistic treatment conditions, we found that subjects with higher 5-HT_{1A} were less likely to remit after 1 year of treatment [45]. Genetic [46] and animal [47] studies also suggest higher 5-HT_{1A} may be associated with poorer treatment response. Similar to Spindelegger *et al.* [48], we have also found decreases in 5-HT_{1A} BP_F in NRM subjects following acute SSRI treatment [49], which again is consistent with the underlying mechanism of action of SSRIs. Lastly, we reported higher 5-HT_{1A} within a cohort of subjects who were currently remitted from a major depressive episode, suggesting higher 5-HT_{1A} expression could be a trait feature of MDD [16]. Thus, if future prospective studies are able to replicate these findings, 5-HT_{1A} imaging could aid in treatment development, approach and planning.

Having characterized many aspects of the [¹¹C]WAY ligand over several years, it is our assertion that modelling and reference region choices can significantly influence the results and

interpretations of studies. For [¹¹C]WAY and other ligands, it is imperative to conduct and evaluate full kinetic modelling prior to using reference tissue methods, which require several assumptions. In the case of [¹¹C]WAY, the reference tissue assumptions cannot be made and full arterial sampling or comparable estimates of input function are necessary to describe the data optimally. However, a new agonist 5-HT_{1A} ligand, [¹¹C]CUMI-101, may be more amenable to reference tissue modelling [50]. Using reference tissue methods or simulated annealing [51,52] to estimate input function, the need for arterial sampling would be eliminated, thereby reducing the subject burden. Ideally, this would make it easier to obtain quantitative data in larger samples, which are needed to better explore genetic and treatment effects on 5-HT_{1A} expression.

Various subtypes of MDD could also be better classified and described in larger samples. Under the current Diagnostic and Statistical Manual-IV description, MDD can be diagnosed by meeting five of nine criteria [53], which creates 1099 ways to meet criteria for the diagnosis; this implies that there is a great deal of individual variation within a MDD cohort. A dimensional approach to symptom categorization, as that proposed under the Research Domain Criteria [54,55] initiative, may help better describe subject groups in future studies. Focusing on symptom clusters across diagnostic groups may benefit treatment prediction studies and identification of biomarkers by decreasing the variance inherent in studying diagnostic groups. Eventually, with the application of careful methodology, quantification and hope of identifying treatment predictors, it may be possible to bring serotonergic imaging of the 5-HT_{1A} and other receptors into clinical use.

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