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Higher 5-HT_{1A} autoreceptor binding as an endophenotype for major depressive disorder identified in high risk offspring – A pilot study

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ABSTRACT

Higher serotonin-1A (5-HT_{1A}) receptor binding potential (BP_F) has been found in major depressive disorder (MDD) during and between major depressive episodes. We investigated whether higher 5-HT_{1A} binding is a biologic trait transmitted to healthy high risk (HR) offspring of MDD probands. Data were collected contemporaneously from: nine HR, 30 depressed not-recently medicated (NRM) MDD, 18 remitted NRM MDD, 51 healthy volunteer (HV) subjects. Subjects underwent positron emission tomography (PET) using [^{11}C] WAY100635 to quantify 5-HT_{1A} BP_F, estimated using metabolite, free fraction-corrected arterial input function and cerebellar white matter as reference region. Multivoxel pattern analyses (MVPA) of PET data evaluated group status classification of individuals. When tested across 13 regions of interest, an effect of diagnosis is found on BP_F which remains significant after correction for sex, age, injected mass and dose: HR have higher BP_F than HV (84.3% higher in midbrain raphe, 40.8% higher in hippocampus, mean BP_F across all 13 brain regions is 49.9% ± 11.8% higher). Voxel-level BP_F maps distinguish HR *vs.* HV. Elevated 5-HT_{1A} BP_F appears to be a familially transmitted trait abnormality. Future studies are needed to replicate this finding in a larger cohort and demonstrate the link to the familial transmission of mood disorders.

1. Introduction

Depressive disorders are estimated to be 40% heritable (Uhl and Grow, 2004), and offspring of individuals with early-onset depression are at higher risk of developing these disorders (Mann et al., 2005). The serotonin (5-HT) system has been implicated in major depressive disorder (MDD) (Blier et al., 1990), and offspring of MDD patients report transient depression after serotonin depletion by acute tryptophan depletion (Klaassen et al., 1999). An endophenotype of MDD may help to identify persons at elevated risk of developing MDD (HR or high risk) while still healthy (no history of a mood disorder). A biomarker or endophenotype could also: (a) improve diagnostic classification by identification of biologic subtypes; (b) improve treatment outcome if biologic subtypes respond to different treatments; (c) guide the search for genetic and environmental factors that mediate the vulnerability to mood disorders and are modifiable to inform a prevention strategy; and (d) help develop and validate animal models of depression.

We have previously reported elevated serotonin-1A (5-HT_{1A}) receptor binding in MDD during a major depressive episode (MDE) across 13 brain regions known to have high 5-HT_{1A} receptor density (Parsey et al., 2010a, 2006). Most studies (Bhagwagar et al., 2004; Drevets et al., 1999Drevets et al., 2007; Sargent et al., 2000; Shively et al., 2006) have not replicated our findings, but we have demonstrated that a key contributor to divergent findings is the choice of outcome measure of binding potential (BP_F, BP_{ND}, or BP_P, as defined using published consensus nomenclature (Innis et al., 2007)) and reference region (RR) (Parsey et al., 2010a). Two studies in depressed humans ($N = 16$ (Drevets et al., 2007), $N = 25$ (Sargent et al., 2000)) and one study in

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depressed non-human primates ($N = 17$ (Shively et al., 2006)) that showed decreased 5-HT_{1A} receptor binding used BP_{ND} as outcome measure and cerebellum as the RR, including cerebellar gray matter of the vermis, the part of the cerebellum with the highest specific binding which has been shown to influence the direction of the findings (Parsey et al., 2010a). Briefly, when BP_{ND} is used as an outcome measure as opposed to BP_P, it is more likely to find a decrease in BP_{ND} because the total volume of distribution in the RR ($V_{T(RR)}$) of [^{11}C]WAY100635 is less than 1. Since BP_{ND} (but not BP_P) is estimated by dividing by $V_{T(RR)}$, having a fraction in the denominator makes this formula sensitive to any increase in the estimation of $V_{T(RR)}$ caused by including cerebellar gray matter (which has measurable specific binding) in the delineation of the RR (Hesselgrave and Parsey, 2013; Parsey et al., 2010a, 2000; Slifstein et al., 2000). One study that used cerebellar white matter as the RR showed decreased BP_P but not BP_{ND} in MDD ($N = 20$ (Hirvonen et al., 2008)).

Higher 5-HT_{1A} receptor binding potential (BP_F) is also present in remitted MDD when between episodes and unmedicated (Miller et al., 2009; Parsey et al., 2010b, 2006), suggesting that this finding is a biologic trait marker of MDD.

In the current pilot study to determine whether this biologic trait is present in HR subjects prior to developing clinically significant morbidity (and therefore, highly likely to be an endophenotype), we compared 5-HT_{1A} receptor BP_F in HR subjects to that in healthy volunteers (HV), depressed not-recently medicated (NRM) MDD and remitted NRM MDD subjects. We also employed supervised machine learning analyses of our imaging data seeking classification of HR subjects into either MDD or HV groups based on differences between depressed NRM MDD subjects *vs.* HV and remitted NRM MDD subjects *vs.* HV. Clinical follow-up of a subgroup of HR subjects allowed a preliminary comparison of BP_F between those who did and did not subsequently develop MDD (converters *vs.* non-converters or resilient HR subjects).

2. Methods and materials

2.1. Subjects

Data from nine HR, 30 unrelated depressed NRM MDD, 18 unrelated remitted NRM MDD subjects, and 51 HV were analyzed for this pilot study. The data from HV and all NRM MDD subjects are presented for comparison purposes but were previously published (Kaufman et al., 2015; Parsey et al., 2010a). The HR sample was recruited and their PET data were acquired contemporaneously with the comparison groups: HV, depressed NRM MDD, and remitted NRM MDD. Subjects were recruited through print and online advertisements and referral from our clinical populations.

Subjects were classified as HR if they had no lifetime or current history of a DSM-IV psychiatric illness based on a structured clinical interview (SCID I) (First et al., 1995) and had one or more first-degree relatives with a history of early-onset (<30 years of age) MDD. Five subjects reported having one first-degree relative with a history of MDD (a parent in all cases), and four reported having two or more (*i.e.*, at least one parent and a sibling). No subject confirmed a history of depression in both parents. All subjects provided consent for the Principal Investigator to contact their relative(s) with a history of MDD to confirm their reports. Research interviews were conducted by clinical raters holding Master's degrees or higher. Assessment instruments used for ascertaining family history of mood disorders included a baseline demographic interview, the Childhood Experiences Questionnaire (CEQ)-Modified Abuse History, the Family History for Genetic Studies (FIGS), and the Parental Bonding Instrument (PBI).

Additional inclusion criteria included: age between 18 to 32 years, absence of history of treatment with psychotropic medication, taking no other medications impacting the serotonin system for a minimum of 6 months or any anticoagulant medication for a minimum of 10 days. Exclusion criteria consisted of: current or past MDE or other Axis I psychiatric diagnosis, current or past alcohol or drug use disorder, history of IV drug use or ecstasy use more than twice, family history of schizophrenia, significant active physical illness, lacking capacity to consent, pregnancy, presence of metal implants or a medicinal patch, medical or occupational radiation exposure within the past 12 months, or a head injury causing loss of consciousness for more than three minutes. New York State Psychiatric Institute/Columbia Institutional Review Board-approved written informed consent was obtained from all subjects after they were given a description of the study.

2.2. Radiochemistry and input function measurement

Preparation of [^{11}C]WAY100635 was performed as previously described (Parsey et al., 2000). Between 96.2 and 732.6 MBq of [^{11}C]WAY100635 were injected (Supplementary Table 1). Mean injected mass (μg) differed across groups ($F = 9.00$, $df = 2, 87$, $p < 0.001$); a pairwise post hoc test revealed that the HV group received higher mass than the depressed NRM MDD and HR groups, which received comparable mass. Though we have shown that injected mass in this range does not correlate with binding potential (Miller et al., 2009), we adjusted for injected mass in the analyses.

Arterial plasma radioactivity, metabolites, and plasma free fraction (f_P) were collected and assayed as previously described (Parsey et al., 2006,2000). Unmetabolized parent fraction levels were fit with a Hill function (Wu et al., 2007). The input function was corrected for unmetabolized tracer by multiplying the total plasma counts with the interpolated parent fraction. The metabolite-corrected arterial input function was fit as the combination of a straight line and the sum of three decreasing exponentials, describing the function before and after the peak, respectively.

2.3. Image acquisition and analysis

PET image acquisition protocol details have been previously described (Parsey et al., 2010a, 2006, 2000). Briefly, venous and arterial catheters were used to inject radiotracer and to obtain arterial samples for the input function, respectively. The head was immobilized using a polyurethane head holder system (Soule Medical; Tampa, FL, USA). PET imaging was performed using an ECAT Exact HR + (Siemens/CTI; Knoxville, TN, USA). Data were collected in 3D mode for 110 min in 20 frames of increasing duration: 3 at 20 s, 3 at 1 min, 3 at 2 min, 2 at 5 min and 9 at 10 min.

Images were reconstructed, using attenuation correction from the transmission data, to a 128 × 128 matrix (pixel size: 1.72 × 1.72 mm). A model-based method was used to correct scatter (CC et al., 1996). A Shepp filter of 0.5 (2.5 mm in full width at half maximum, FWHM) was used for the reconstruction and estimated image. The Z filter was all-pass 0.4 (2.0 mm in FWHM), and the zoom factor was 4.0, leading to a final image resolution of 5.1 mm at FWHM at the center of the field of view (Mawlawi et al., 2001).

The last 12 frames of each pilot study were registered to the eighth frame using the FMRIB linear image registration tool (FLIRT) version 5.0 (FMRIB Image Analysis Group, Oxford, UK). Linear co-registration was performed between the averaged motion-corrected PET frames and the MRI as previously described (DeLorenzo et al., 2009).

Acquisition of T1-weighted MRI images for co-registration of PET images and identification of regions of interest (ROIs) was performed as previously described using a 3T Signa HDx system (General Electric Medical Systems; Milwaukee, WI, USA) (Milak et al., 2010). Regional delineations were obtained automatically for all ROIs except for dorsal raphe nucleus (RN), which was manually located on each PET image and delineated by a fixed-volume (20 mm^3) elliptical ROI (Parsey et al., 2010aParsey et al., 2006). Automatic ROIs were obtained using non-linear registration techniques to warp 18 manually outlined MRIs. The 18 templates were registered to the skull-stripped (using Atropos, (Avants et al., 2011)) target brain MRI using the Automatic Registration