Published in final edited form as:

Neurosci Biobehav Rev. 2009 July ; 33(7): 1109–1132. doi:10.1016/j.neubiorev.2009.05.005.

The dopaminergic basis of human behaviors: a review of molecular imaging studies

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Abstract

This systematic review describes human molecular imaging studies which have investigated alterations in extracellular DA levels during performance of behavioral tasks. Whilst heterogeneity in experimental methods limits meta-analysis, we describe the advantages and limitations of different methodological approaches. Interpretation of experimental results may be limited by regional cerebral blood flow (rCBF) changes, head movement and choice of control conditions. We revisit our original study of striatal DA release during video-game playing (Koepp et al., 1998) to illustrate the potentially confounding influences of head movement and alterations in rCBF. Changes in [¹¹C]raclopride binding may be detected in extrastriatal as well as striatal brain regions – however we review evidence which suggests that extrastriatal changes may not be clearly interpreted in terms of DA release. Whilst several investigations have detected increases in striatal extracellular DA concentrations during task components such as motor learning and execution, reward-related processes, stress and cognitive performance, the presence of potentially biasing factors should be carefully considered (and, where possible, accounted for) when designing and interpreting future studies.

Keywords

Dopamine; PET; SPET; striatum; D2/3 receptor; [¹¹C]raclopride; cognition; reward; stress; motor

Introduction

In 1998, we reported increased dopamine (DA) release in man during performance of a behavioral task (Koepp et al., 1998) using positron emission tomography (PET). In the presence of the DA D_{2/3} receptor radiotracer [¹¹C]raclopride, volunteers played a videogame in which a tank had to be successfully steered around a battlefield arena to collect flags and obtain a monetary reward. Decreased [¹¹C]raclopride binding, consistent with increased DA release, was observed in the striatum of subjects whilst playing the videogame in comparison to a rest condition. This study demonstrated DA release during normal human

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behavior for the first time, and set the stage for non-invasive investigation of the role of DA in processes such as learning, reward and sensorimotor integration. As will be reviewed here, literature describing the dopaminergic basis of human behavior is now rapidly expanding and DA release has been specifically associated with several motor, reward-related and cognitive functions. In parallel, the past decade has seen much refinement and evolution of methodological approaches to measuring DA release using D_{2/3} radiotracers using PET and the related technique, single photon emission tomography (SPET).

From a historical perspective, suggestions that select DA receptor radiotracers may be used to image changes in extracellular DA levels began in 1989, with publication of *ex vivo* data demonstrating the sensitivity of D_{2/3} receptor radiotracers to changes in endogenous DA levels (Ross et al., 1989a; Ross et al., 1989b; Seeman et al., 1989). Indications that this sensitivity could also be observed *in vivo* using positron emission tomography (PET) technology rapidly followed, when increased displacement of the D_{2/3} tracer (¹⁸F)-N-methylspiroperidol was observed following administration of the anticholinergic benztropine to baboons (Dewey et al., 1990). This finding was subsequently confirmed by applying the same technique to investigate amphetamine-induced DA release (Dewey et al., 1991). Landmark investigations in humans followed swiftly afterwards; data showing decreases in binding of the D_{2/3} receptor PET radiotracer [¹¹C]raclopride in response to administration of amphetamine were published in 1992 (Farde et al., 1992) and similar results were subsequently obtained following administration of the DA re-uptake inhibitor methylphenidate (Volkow et al., 1994).

The ability of D_{2/3} receptor radiotracers to index DA release *in vivo* is commonly described by the ‘classical occupancy model’; D_{2/3} receptor radiotracers compete with DA for receptor binding, thus a decrease in radiotracer binding potential (BP) is interpreted as an increase in DA release (see (Laruelle 2000a)). The amount of radiotracer present in a particular brain region of interest (ROI) can be detected using PET and SPET. The specific binding of the radiotracer to receptors is then inferred through careful modeling of radiotracer kinetics. These techniques, used in combination with administration of pharmacological compounds that target non-dopaminergic neurotransmitter systems, have allowed examination of the neuropharmacology of DA release in the human brain (Breier et al., 1998; Brody et al., 2004; Dewey et al., 1993; Vollenweider et al., 1999), and studies employing pharmacological challenges which release DA (e.g. amphetamine), reveal much about the neurochemistry of many brain disorders (Abi-Dargham et al., 1998; Breier et al., 1997; Laruelle et al., 1996; Laruelle et al., 1999; Piccini et al., 2003; Rosa et al., 2002; Singer et al., 2002; Volkow et al., 1997; Volkow et al., 2007). However, the ability to study DA release produced by ethologically-relevant, non-pharmacological stimuli is of greater functional relevance in terms of investigating the dopaminergic basis of human behavior and its role in disease mechanisms.

The possibility that D_{2/3} radiotracer PET techniques might prove sensitive enough to measure the relatively smaller changes in DA release expected following non-pharmacological interventions was first proposed in 1995 following detailed review of dopaminergic neurophysiology and integration of these parameters into simulations (Fischer et al., 1995; Morris et al., 1995). Encouraged by the positive results of these simulations, we performed our initial study of DA release during videogame playing and observed significant decreases in [¹¹C]raclopride BP (Koepp et al., 1998).

Since the publication of our original finding (Koepp et al., 1998), there have been a large number of studies in this field, employing a number of different approaches, and there is no clear consensus as to the best method. The aim of this paper is to systematically review the molecular imaging studies of DA release in man and to critically appraise the

methodological approaches used. In addition, we re-analyze our original data to evaluate and illustrate the degree to which certain methodological factors may alter findings. We conclude by reviewing the findings of molecular imaging studies of non-pharmacologically-evoked changes in DA release in man, and summarize what these studies have told us about the role of DA in aspects of human behavior.

As studies in experimental animals have since significantly increased our understanding of dopaminergic neurophysiology, we begin this review by describing components of this system relevant to measuring non-pharmacologically-induced changes in DA release using D_{2/3} receptor radiotracers and PET methodology. We then present the findings of our systematic review and re-evaluation of previous data.

Neurophysiology of the dopaminergic system

Electrophysiological recording shows that, at 'baseline', action potentials occur in mesostriatal DA neurons at a frequency of about 4Hz, referred to as tonic or 'pacemaker' firing (Grace et al., 1984b). On presentation of a reward, a stimulus predicting a reward, a novel arousing stimulus, or a stressful stimulus, a short burst in DA neuron firing rate occurs (Anstrom and Woodward., 2005; Carelli et al., 1994; Grace et al., 1984a; Hyland et al., 2002; Schultz et al., 1988; Steinfels et al., 1983). These bursts in action potential frequency are associated with transient increases in extracellular DA concentrations, which can be measured invasively using amperometry or cyclic voltammetry (Dugast et al., 1994; Garriss et al., 1994; Venton et al., 2003; Wightman 2006). In contrast, changes in the level of tonic DA release, occurring through alterations in dopaminergic neuron population activity (the proportion of spontaneously active DA neurons) or presynaptic modulation, can be measured invasively using microdialysis (Floresco et al., 2003). Released DA is then removed from the extracellular space through diffusion and re-uptake via dopamine transporters (DATs) (Cragg et al., 2004).

Computational models suggest that phasic DA may provide a 'teaching signal' for reward-based learning and the selection of actions which will maximize reward delivery (Bayer et al., 2005; Dayan et al., 2002; Montague et al., 1996; Montague et al., 2004; Schultz, 1997). Changes in tonic DA levels have been suggested to enable or energize behavior and vigor of responding (Niv 2007). Changes in PET radiotracer BP presumably reflect net alterations in extracellular DA - resulting from both tonic and phasic DA release (although see Grace, 2008), and also DA re-uptake and diffusion.

Relationship between extracellular dopamine levels and D₂ radiotracer binding

A somewhat counterintuitive finding from PET studies of task-induced DA release is that the magnitude of change detected in many studies is similar to that observed following administration of psychostimulants such as amphetamine. Microdialysis studies in rats have shown that non-pharmacological stimuli, such as transfer to a novel environment, increase DA levels in the ventral striatum (nucleus accumbens), to an order of approximately 20% (Neigh et al., 2001), whilst amphetamine administration may increase extracellular DA levels by around ~1500% (e.g. (Schiffer et al., 2006). Dual microdialysis and PET studies have demonstrated that the ratio of magnitude of change in extracellular DA to the magnitude of change in [¹¹C]raclopride binding varies according to the stimulus applied (Breier et al., 1997; Schiffer et al., 2006; Tsukada et al., 1999). D₂ antagonist radiotracer displacement generally does not exceed about 40-50% (Kortekaas et al., 2004; Laruelle 2000a). At a basic level, this ceiling effect relates to the fact that there are a limited number of D₂ receptors in the striatum.

In vitro studies of D₂ receptors reveal the existence of intraconvertible high (D_{2high}) and low (D_{2low}) affinity states for agonist binding; the D_{2high} state is regarded as the functional state due to G-protein coupling (Sibley et al., 1982). Whilst antagonists have equal affinity at both receptor states, agonists have greater affinity for the D_{2high} (1-10 nM) than the D_{2low} state (0.7-1.5 μ M) (Freedman et al., 1994; Richfield et al., 1989; Seeman et al., 2003; Sibley et al., 1982; Sokoloff et al., 1990; Sokoloff et al., 1992). Based on this *in vitro* data and *in vivo* estimates of baseline D₂ occupancy by DA and the proportion of receptors in the high affinity state, models have been proposed which attempt to explain the ceiling effect in D₂ PET data (Laruelle 2000a; Narendran et al., 2004). These models estimate that the proportion of D₂ antagonist radiotracer binding susceptible to competition by DA is ~38%.

Recently, D_{2/3} agonist radiotracers have been developed in the hope that they may be more sensitive than D_{2/3} antagonist radiotracers in detecting fluctuations in DA, as a greater degree of competition will occur at the same site (Cumming et al., 2002; Hwang et al., 2000; Mukherjee et al., 2000; Mukherjee et al., 2004; Shi et al., 2004; Wilson et al., 2005; Zijlstra et al., 1993). Increased sensitivity of D_{2/3} agonist radiotracers to changes in extracellular DA has yet to be confirmed in man; an initial study exploring the sensitivity of the D_{2/3} agonist radiotracer [¹¹C]PHNO to amphetamine-induced changes in DA showed a sensitivity which was similar or, at most, only marginally greater than that previously observed with [¹¹C]raclopride (Willeit et al., 2008).

The relationship between D_{2/3} radiotracer binding and extracellular DA levels may also reflect agonist-dependent receptor internalization (Goggi et al., 2007; Laruelle 2000a; Sun et al., 2003) and/or D₂ monomer-dimer equilibrium (Logan et al., 2001a). As will be discussed in more detail below, the kinetics of changes in extracellular DA relative to D_{2/3} radiotracer kinetics may also be important in determining the degree of change in radiotracer binding potential (Morris et al., 2007; Yoder et al., 2004). Therefore whilst changes in BP of D_{2/3} radiotracers such as [¹¹C]raclopride clearly show a dose-dependent relationship with extracellular DA levels, the nature of this relationship is complex and linearity may vary according to the type of stimulus applied.

Competition may be predominantly extrasynaptic

Throughout the D_{2/3} PET literature it is often assumed that most D_{2/3} receptors are synaptic and D_{2/3} radiotracer PET therefore measures synaptic DA transmission. However, this interpretation must be reconsidered as several studies show that the location of D_{2/3} receptors, and also DATs, is *predominantly extrasynaptic* (Ciliax et al., 1995; Cragg et al., 2004; Hersch et al., 1995; Sesack et al., 1994; Yung et al., 1995; Zoli et al., 1998). This is accordant with the well accepted view that DA acts via volume transmission in the striatum (Fuxe et al., 2007; Zoli et al., 1998). After phasic release, DA may diffuse several microns from the release site (Gonon et al., 2000; Peters et al., 2000; Venton et al., 2003); a distance far larger than the width of the synaptic cleft (about 0.5 μ m) (Groves et al., 1994; Pickel et al., 1981). DA concentrations within the synaptic cleft may transiently rise to 1.6 mM (Garris et al., 1994), and recorded extrasynaptic DA concentrations arising from natural DA transients or following electrical stimulus pulses in rodents range from ~ 0.2-1 μ M (Garris et al., 1994; Gonon 1997; Robinson et al., 2001; Robinson et al., 2002; Venton et al., 2003).

Recent models of DA striatal transmission predict that activation of D_{2high} receptors after release of a single DA vesicle may occur at a maximum effective radius of diffusion of up to 7 μ m, whereas concentrations of 1 μ M, capable of binding low affinity receptors, are associated with a maximum effective radius of <2 μ m; both values far exceed the dimensions of the synaptic cleft (Cragg et al., 2004; Rice et al., 2008). Further analysis shows that, for D_{2high} receptors, DA released from one synapse may influence receptors (whether intra- or extra-synaptic) in the vicinity of 20-100 DA synapses within this radius

(Cragg et al., 2004; Rice et al., 2008). These kinetic analyses have resulted in the proposal of a new model of striatal DA synapses (Rice et al., 2008), which accounts for significant spill over of DA to the extrasynaptic space and the predominant activation of extrasynaptic over intrasynaptic D₂ receptors. Although this model requires further evaluation, it would appear that extrasynaptic receptors play a significant if not predominant role in the binding and displacement D_{2/3} radiotracers in the striatum.

Competition may occur within anatomically distinct striatal subdivisions

The striatum is commonly divided into three anatomical subdivisions; the caudate nucleus, putamen and ventral striatum. Whilst the dorsal striatum (neostriatum) includes the major proportion of the caudate nucleus and putamen, the ventral striatum is composed of the nucleus accumbens, part of the olfactory tubercle and the most ventromedial portions of the caudate and putamen. The dorsal striatum primarily receives DA fibres from the substantia nigra, whilst the origin of DA input to the ventral striatum lies principally in the ventral tegmental area (VTA). DA neurons are innervated by glutamatergic afferents from cortical areas, which modulate DA release at the cell body and terminal level (Cheramy et al., 1986; Karreman et al., 1996; Leviel et al., 1990; Murase et al., 1993; Taber et al., 1993; Taber et al., 1995). Cortical inputs to the striatum are topographically organised, forming parallel cortico-striatal-thalamo-cortical loops (Alexander et al., 1986). These loops are organized along a dorsolateral to ventromedial gradient, which may functionally relate to motor, cognitive and reward processes (Haber et al., 2000). Generally speaking, anatomical studies in non-human primates show that the motor and premotor cortices project to the putamen (Flaherty et al., 1994), whilst the head of the caudate receives input from the prefrontal cortex (Selemon et al., 1985) and the ventral striatum receives projections from the orbital and medial frontal cortex (Kunishio et al., 1994).

These anatomical subdivisions have also been conceptualized as ‘functional subdivisions’ (sensorimotor, associative and limbic) for PET image analysis (Martinez et al., 2003). This model should be viewed as probabilistic rather than exclusive due to significant overlap (Martinez et al., 2003) and as delineation may also be limited by scanner resolution and partial volume effects (Drevets et al., 2001; Mawlawi et al., 2001). The most convincing evidence that PET can detect changes in DA release in functionally discrete areas of the striatum is provided in the repetitive transcranial magnetic stimulation (rTMS) studies of Strafella and colleagues (Strafella et al., 2001; Strafella et al., 2003; Strafella et al., 2005). Stimulation of the mid-dorsolateral PFC caused a selective decrease in [¹¹C]raclopride binding in the head of the caudate nucleus (Strafella et al., 2001). The opposite pattern was observed when the motor cortex was stimulated; decreases in [¹¹C]raclopride binding were observed in the putamen but not other striatal areas (Strafella et al., 2003; Strafella et al., 2005). These findings are in accordance with anatomical studies of cortico-striatal projections in primates (Flaherty et al., 1994; Kunishio et al., 1994; Selemon et al., 1985) and suggest that spatially distinct areas of increased DA release as imaged with PET may be functionally related to the discrete behavioral process under investigation.

Methodological aspects in imaging DA release

Choice of radioligand

Currently, D_{2/3} receptor binding in the striatum is normally quantified using either the PET radioligand [¹¹C]raclopride, or the single photon emission tomography (SPET) radioligands [¹²³I]IBZM and [¹²³I]epidepride. These D₂ antagonist radiotracers are readily displaceable by increases or decreases in endogenous DA (Endres et al., 1998; Laruelle 2000a). Other D₂ antagonist radiotracers such as spiperone and D1 radiotracers are not readily vulnerable to changes in extracellular DA due to factors such as receptor internalisation (Laruelle 2000a),

monomer-dimer formation (Logan et al., 2001b) or tracer kinetics (Morris et al., 2007) as mentioned above. Recent images obtained with the newly developed D_{2/3} agonist radiotracer [¹¹C]PHNO demonstrate higher binding in the ventral portion of the striatum and globus pallidus compared to [¹¹C]raclopride (Willeit et al., 2006), which may be attributable to a higher affinity of [¹¹C]PHNO for D₃ over D₂ receptors (Narendran et al., 2006). Although not yet confirmed in human volunteers, [¹¹C]PHNO may therefore offer some particular advantage in assessing changes in DA release in the ventral aspect of the striatum, as DA also has higher affinity for the D₃ over D₂ receptor subtype (Sokoloff et al., 1990). As addressed in detail below, in order to measure extrastriatal D₂ receptor availability and possibly extrastriatal DA release, high affinity antagonist radiotracers such as [¹¹C]FLB457 and [¹⁸F]fallypride are required (Aalto et al., 2005; Montgomery et al., 2007; Riccardi et al., 2006a; Riccardi et al., 2006b; Slifstein et al., 2004).

Methods and results of systematic

To identify all PET and SPET studies of non-pharmacologically evoked DA release, Medline and PubMed bibliographic databases were searched using the keywords “dopamine,” “emission tomography,” “task,” “stress,” “reward,” “motor,” “cognitive”. We also hand-searched references within publications. We selected studies where PET or SPET was used to infer changes in extracellular DA concentrations in man following application of non-pharmacological stimuli relative to a control condition. Using this search strategy, we identified 44 publications, published from 1998 to April 2009, as listed in Table 1.

Experimental design

As presented in Table 1, several methodological and analytical approaches have been applied in [¹¹C]raclopride studies of DA release following behavioral challenges which have different practical and methodological advantages and disadvantages. Changes in DA release may be inferred using either ‘blocking’ or ‘displacement’ studies. In blocking studies, radiotracer binding is measured under a DA activation (‘challenge’) condition and control condition, where the changes in D_{2/3} receptor occupancy are induced before radiotracer administration (Laruelle 2000a). Magnitude of DA release is then inferred through subtraction of the control from the activation condition. Sessions are typically performed on separate days and [¹¹C]raclopride is usually administered as a bolus dose. This is perhaps the most commonly adopted approach to investigation of striatal DA release (see Table 1).

There are also methods which measure DA release during a single scan session; this design has several practical advantages, such as the requirement for only a single radiochemical synthesis and administration and avoidance of session effects. These are termed ‘displacement’ studies as the activation paradigm commences after radiotracer administration. Here, [¹¹C]raclopride may be administered by an initial bolus followed by constant infusion (termed the bolus infusion (BI) method) to maintain radiotracer equilibrium, during which both control and activation data are collected (Carson et al., 1997; Watabe et al., 2000). We have previously adopted the BI approach in investigation of stress-induced DA release (Montgomery et al., 2006a), and it has also been used by other groups in investigation of DA release during application of painful stimuli (Scott et al., 2006; Scott et al., 2007b; Scott et al., 2008) and motor learning (Garraux et al., 2007). Displacement studies may also be performed using a single bolus administration of [¹¹C]raclopride. Here, dynamic scan data is used to measure hypothesized increases in the washout of the radiotracer elicited by DA released during the activation paradigm (Alpert et al., 2003; Pappata et al., 2002). This approach has been applied to investigations of DA release during

performance of reward (Pappata et al., 2002) and motor tasks (Badgaiyan et al., 2003; Badgaiyan et al., 2007; Badgaiyan et al., 2008).

In order to discuss the relative merits and disadvantages of these approaches in further depth, a brief description of the different approaches in radiotracer pharmacokinetic modeling is required. For a detailed description of these models, the reader is directed to the review of (Slifstein et al., 2001), and the original methodological papers cited in the following sections. Here we focus specifically on methods that have been applied to measurement of DA release during behavioral paradigms (as detailed in Table 1) and direct discussion to physiological aspects such as the dynamics of increased DA release, changes in blood flow and head movement that may be particularly pertinent to behavioral activation paradigms.

The PET approach to detecting endogenous transmitter release (in this case DA) is based on the estimation of changes in the concentration of available neuroreceptor sites (B_{avail}), which occur in response to the associated changes in the local neurotransmitter concentration according to the Michaelis-Menten equation. The kinetic behavior of the radioligand (e.g. [^{11}C]raclopride) is in turn dependent on B_{avail} , and is linear at tracer concentrations. This enables the determination of a binding potential (BP). BP equals the ratio of the specifically bound radioligand over the free concentration of radioligand in the brain at equilibrium. In vitro, in the absence of competing ligands, BP is equal to the density of radiotracer binding sites (B_{max}) divided by the radiotracer affinity (K_D) (Mintun et al., 1984). In practice, in PET studies, BP is defined either as the ratio at equilibrium between specifically bound tracer and that in the free and non-specifically bound compartments (this is denoted BP_{ND}) or relative to that in plasma, denoted BP_{PP} (Innis et al., 2007). Changes in BP_{ND} , (or BP_{PP}) in activation studies are usually assumed to reflect changes in B_{avail} , rather than in the K_D for the radiotracer, and a decrease in BP_{ND} is assumed to reflect increased endogenous neurotransmitter release.

BP_{ND} is an equilibrium concept, but may be estimated from dynamic PET studies, as well as equilibrium PET studies when a suitable reference region, devoid of specific binding sites is available. An input function describing the time course of the delivery of the radiotracer to the tissue is required for quantification of dynamic studies, but to avoid the need for arterial sampling, the plasma input function may be substituted, where possible, by the tracer time course in the reference region itself. For [^{11}C]raclopride, the cerebellum may be used (Gunn et al., 1997; Hume et al., 1992; Lammertsma et al., 1996b; Logan et al., 1996). We are not aware of any PET studies of task-induced DA release that have used an arterial input function; likely due to methodological simplicity, all studies listed in Table 1 have adopted the reference region approach. For the two [^{123}I]IBZM SPECT studies of task-induced DA release (Larisch et al., 1999; Schommartz et al., 2000), reference ROIs in cortical regions were preferred.

The BI technique confers significant advantage as, once equilibrium is reached, BP_{ND} may be calculated as the ratio of the concentration of the radiotracer in the ROI to the concentration of the radiotracer in the reference region: ($\text{BP}_{\text{ND}} = (\text{C}_{\text{ROI}} - \text{C}_{\text{REF}})/\text{C}_{\text{REF}}$). Whilst this approach has the advantage of being relatively simple compared to the analysis methods applied to dynamic bolus studies (Carson 2000), changes in BP_{ND} may be long-lasting (Carson 2000; Houston et al., 2004), meaning that, if the single BI scan approach is used, the control and challenge conditions can seldom be counterbalanced. Thus, the challenge condition usually occurs in the second part of the scan where the statistical quality of the data is in decline due to radioactive decay (Martinez et al., 2003). However, counterbalancing may be possible for some non-pharmacological challenges (Scott et al., 2007b), presumably as the smaller magnitudes of DA concentration change (compared to

that resulting from amphetamine administration, for example) do not markedly result in secondary processes such as receptor internalization, which may lead to sustained decreases in BP (Laruelle, 2000).

When the radiotracer is administered as a bolus injection only, transient equilibrium may be assumed when maximal values for specific binding are obtained (Farde et al., 1989); this occurs approximately 20-25 minutes after rapid bolus injection of [^{11}C]raclopride (Ito et al., 1998). In contrast to the BI approach, equilibrium is not sustained as the radiotracer begins to washout of the tissue, and BP must be derived using model-based methods such as graphical analysis (Logan et al., 1990; Logan et al., 1994; Logan et al., 1996) or compartmental kinetic analysis (Farde et al., 1989; Lammertsma et al., 1996b) which relate time-activity curves in the ROI to those of the arterial or reference region tracer input function (TIF). The multi-time graphical analysis method for reversible tracers, also called a Logan plot, provides, via linear regression, a distribution volume ratio (DVR), where $\text{DVR} = \text{BP}_{\text{ND}} + 1$ (Logan et al., 1990; Logan et al., 1996). In behavioral studies, this method has been used in the investigations of task-induced DA release performed by Volkow and colleagues (Volkow et al., 2002b; Volkow et al., 2004; Volkow et al., 2006; Wang et al., 2000). The Logan method has the advantage that a compartmental model does not need to be specified *a priori*, but has been criticized on the basis that statistical noise may bias parameter estimates (Slifstein et al., 2000).

As shown in Table 1, the majority of investigations into task-induced DA release have employed the simplified reference tissue model (SRTM), which combines compartmental analysis with a cerebellar TIF (Gunn et al., 1997; Lammertsma et al., 1996a; Lammertsma et al., 1996b). Compartmental kinetic models such as the SRTM describe the concentrations of the radiotracer in different physiological compartments (such as plasma, free and non-specifically bound and specifically bound compartments) and the rate constants of radiotracer transfer between these compartments to give estimates of radiotracer BP (Mintun et al., 1984). With specific reference to measurement of task-induced DA release, both the Logan and STRM methods have been criticized on the basis that they assume that DA levels achieve a steady state for the duration over which BP_{ND} is measured, whereas, in reality, many different learning and adaptive processes may be occurring over this time period (Alpert et al., 2003).

In the more recent approaches of Pappata et al., (2002) and Alpert et al., (2003), dynamic models were applied to DA release evoked by cognitive tasks. Theoretically, these approaches which utilize temporal data may be better aligned to the physiological dynamics of extracellular DA as they account for the transient nature of DA released during cognitive tasks. Pappata et al., (2002) created simulated curves for [^{11}C]raclopride displacement and changes in cerebral blood flow to construct a statistical linear model, which was then tested against acquired data on a voxel-wise basis. However, the curves used for the resting state were obtained in previous studies in separate subjects, and simulated curves were used for [^{11}C]raclopride displacement during the task, which may not precisely fit the experimental data (Alpert et al., 2003). We are not aware of any further investigations that have adopted this method.

Alpert et al., (2003) instead used a linear extension of the SRTM (LSSRM) where the model is fitted to individual data, increasing sensitivity so that changes in DA release may be detected in individual subjects. The LSSRM approach was designed to measure time-dependent changes in DA release and has since been applied to detect changes in DA release during unrewarded motor, motor planning, motor sequence learning and motor memory tasks (Badgaiyan et al., 2003; Badgaiyan et al., 2007; Badgaiyan et al., 2008). However, displacement approaches using dynamic scan data from single bolus radiotracer

administrations have been criticized on the basis that task-induced changes in blood flow may elicit alterations in the dynamic [^{11}C]raclopride curve indistinguishable from the effects of increased DA release (Aston et al., 2000; Dagher et al., 1998; Laruelle 2000b), as will be discussed in more detail below.

Minimizing biasing factors

Changes in cerebral blood flow

In developing these methodologies a major consideration has been the influences that task-induced changes in blood flow may exert on the estimation of $D_{2/3}$ radiotracer binding potential. Using hyperventilation to decrease regional cerebral blood flow (rCBF) via vasoconstriction, an [^{11}C]raclopride scan in a single subject showed an apparent decrease in both the distribution volume and transport of the radiotracer to the brain (K_1) (Logan et al., 1994) suggesting that radiotracer delivery may be altered by changes in rCBF. The SRTM returns a similar parameter, R_1 -the delivery of the radiotracer to the striatum relative to the cerebellum (Lammertsma et al., 1996b). Hence, using both the Logan graphical analysis and SRTM methods, rCBF effects are theoretically distinguishable from changes in neurotransmitter release - however, these measures are often not reported. These R_1 or K_1 measures are limited in that transient changes in blood flow during the scanning period, which may also produce artifactual results, are not estimated (Laruelle 2000b).

In the original [^{11}C]raclopride PET study of video-game playing, reductions in R_1 were observed during the activation condition, in addition to the observed decreases in BP (Koepp et al., 1998). These changes in R_1 did not correlate with changes in BP_{ND} and it was concluded that the observed decrease in R_1 may have been due to relatively greater increases in rCBF in the cerebellum compared to the striatum whilst playing the game. This was subsequently confirmed when cerebral blood flow during the task was measured using H_2 - ^{15}O PET (Koepp et al., 2000).

Figure 1A shows the rCBF values measured in the dorsal and ventral striatum and cerebellum during the rest and task periods. During the task period, the largest increases (mean 29%) in rCBF occurred in the cerebellum. Smaller increases in rCBF occurred in the striatal regions during the task period (dorsal striatum 16%; ventral striatum 10%; caudate 9%). Dividing rCBF values in the dorsal and striatal ROIs by that obtained in the cerebellum gives a measure equivalent to R_1 ($\text{CBF}_{\text{ROI/CB}}$). As shown in Figure 1B, $\text{CBF}_{\text{ROI/CB}}$ was reduced by ~10% in the dorsal striatum, and ~15% in the ventral striatum during the task relative to the baseline condition. These figures are therefore consistent with the changes in R_1 that were detected in the original [^{11}C]raclopride PET investigation, where R_1 decreased by a mean 13% in the dorsal striatum and 14% in the ventral striatum (Koepp et al., 1998). The question was therefore to what extent could these changes in flow contribute to the apparent decreases in the estimates of striatal [^{11}C]raclopride BP_{ND} .

Simulations performed by Dagher et al., (1998) of the single dynamic scan displacement approach have shown that if k_2 (the efflux rate constant) is increased more than K_1 , the resulting changes in radiotracer binding are indistinguishable from changes that would result from increased release of DA, potentially resulting in false positive results. However, it can be shown under the assumptions of the Renkin-Crone model with passive transport of a solute between capillary plasma and tissue, that changes in either blood flow rate or the permeability surface product (PS product) for the solute would affect both K_1 and k_2 equally, so that an apparent change in the estimated BP_{ND} is unlikely under steady state conditions. Simulations performed for validation of the displacement methods have demonstrated that when K_1 and k_2 are increased equally, no significant effects on radiotracer binding are detected (Pappata et al. 2002; Alpert et al. 2003). However, increases in rCBF

during the washout period when radiotracer concentration in the blood is minimal will primarily affect efflux and not influx, and it is likely that an increase in rCBF either in the striatum or in the reference region, on commencing the task during the washout period, would lead to biased estimations of BP_{ND} .

Returning to the video game example, Koepp et al. (2000) concluded that since the mean values of CBF in each of the regions were relatively constant during rest and activation periods, use of SRTM was unlikely to induce a bias in the estimated BPs. This conclusion is supported by simulations of the video game experiments taking into account the actual fluctuations for flow and their variation during rest and activated conditions as reported in Figure 1A. In brief, an arterial plasma parent input function for a bolus [^{11}C]raclopride scan was taken from the study of Lammertsma et al. (1996) together with the mean values for the rate constants (K_1 , k_2) describing the fit of cerebellum to a one tissue compartmental model with a plasma input function, as reported by Farde et al. (1989). Equivalent mean PS products were calculated for cerebellum from the mean values for blood flow under rest and activated conditions given in Table 1A, according to the Renkin-Crone model;

$PS = -F \cdot \log(1 - K_1/F)$, where F is the plasma flow rate assuming an haematocrit of 0.4.

It was assumed that the total volume of distribution for [^{11}C]raclopride in cerebellum did not change between rest and task conditions. Values for the PS products and equivalent rate constants for dorsal and ventral striatum were then derived from the mean blood flow under rest conditions (Figure 1A), together with estimates of R_1 and BP relative to cerebellum reported by Koepp et al. (1998) under resting conditions. It was then possible to construct individual time activity curves (TACs) for cerebellum under baseline and test conditions and for striatal regions under baseline conditions taking into account the individual fluctuations in blood flow over the scanning periods. It was also assumed that PS products varied in proportion to flow so as to exaggerate the possible effects of the small fluctuations in blood flow during the scans. Striatal TACs were simulated under test conditions either assuming a decrease in BP as reported by Koepp et al., 1998 or with no change in BP. Estimates of BP were then estimated using the STRM, as in Koepp et al., (1998) which takes no account of bias induced by fluctuations in blood flow. These simulations showed that under the above assumptions there was no confounding effect due to fluctuations in flow; the mean apparent BP_{ND} for ventral striatum would have changed from a baseline value of 2.231 to 2.238 due to blood flow changes alone as opposed to 1.918 given a task induced change in the true BP_{ND} . The corresponding values for dorsal striatum were 2.407, 2.412 and 2.213.

In the present case, a blood flow effect on the apparent changes in BP_{ND} was therefore unlikely, due to the task being initiated prior to scan start and relative constancy of blood flow within each scan. However variations in blood flow during a single scan would result in an underestimation of BP_{ND} had the task been started within the washout period following a single bolus injection and we consider this factor of significant concern in displacement approaches to quantifying changes in DA release. The method least influenced by local or global changes in rCBF is the bolus infusion (BI) approach; once secular equilibrium has been established, the constant levels of the radiotracer in the plasma avoid any confounding effects of blood flow on specific binding values (Carson et al., 1993; Carson et al., 1997; Carson 2000; Endres et al., 1997; Endres et al., 1998). We therefore consider BI radiotracer administration the optimal choice of available methodology when the influences of concurrent changes in rCBF during the scan period are of concern.

Head movement

Head movement may be especially problematic in behavioral studies where volunteers are required to make a verbal or motor response (Montgomery et al., 2006a). Movement during

the scan can markedly reduce the effective scanner resolution (Green et al., 1994) and may lead to inaccurate measurement of BP. Although uncorrected head movement will affect BP measurements obtained using all analysis methods, this may be of particular importance in displacement studies, as it is conceivable that head movement may consistently occur on commencement of the activation task and lead to false positive changes in BP (Dagher et al., 1998). Voxel-wise analysis methods (see below) may also be particularly sensitive to head movement effects, as the binding of [^{11}C]raclopride is much higher in striatal regions compared to the adjacent extrastriatal areas (Zald et al., 2004).

Head movement may be reduced during the scan using restraints such as thermoplastic face masks, as employed by Ouchi et al., (2002) during a motor task and de la Fuente-Fernandez et al., (2001; 2002) in examination of the placebo effect. However, thermoplastic face masks may be uncomfortable for volunteers and previous comparative studies have shown that, although head movement may be considerably reduced, it is not eliminated (Green et al., 1994; Ruttimann et al., 1995). An alternative or complementary approach is to correct effects of head movement *post hoc*, using frame-by-frame (FBF) realignment. Typical FBF realignment techniques align all frames to either an initial or later frame selected on the basis of a high signal-to-noise ratio (Mawlawi et al., 2001; Woods et al., 1992; Woods et al., 1993). The FBF realignment technique is limited by poor statistical quality of data acquired in later frames and an inability to correct for head-movement within frames (which may be up to 10 minutes long) (Montgomery et al., 2006b). In addition, these methods assume that radiotracer distribution is similar in early and late frames; this is not the case following bolus radiotracer administration, which can lead to false positive results (Dagher et al., 1998). To reduce the influence of radiotracer redistribution producing erroneous alignments, the non-attenuation corrected image can be used instead; these images have a higher scalp signal which provides more information for the realignment program to work with (Montgomery et al., 2006a). In addition, denoising using wavelets can be applied to decrease errors introduced by poor signal to noise ratios (Mawlawi et al., 2001; Turkheimer et al., 1999). Recent [^{11}C]raclopride bolus studies of task-induced DA release published by Dagher and colleagues (Hakyemez et al., 2008; Soliman et al., 2008; Zald et al., 2004) use a novel realignment process (Perruchot et al., 2004). Here, brain regions, following automated segmentation from individual MRI images, are assigned generic time-activity curves on the basis of previous data. The frames acquired during the experimental scans are then automatically realigned to target volumes using a realignment algorithm. New methods, such as the use of motion tracking software and movement correction during re-binning of list-mode data, are under development and show superior test-retest reliability (Montgomery et al., 2006b). This approach has only been used in one study of task-related DA release to date (Sawamoto et al., 2008) and may be of particular value in this context as improved reliability of data will increase ability to detect small changes in DA release.

To illustrate the importance of appropriate head-movement correction, we again revisit our original [^{11}C]raclopride bolus video-game data (Koepp et al., 1998). In the original analysis, head movement, although minimized using an orthopedic collar and head support, was not corrected for. Furthermore, striatal ROI were threshold-defined using a fixed-threshold of 40% of the image maximum. This may also produce artifacts; if systematic increases in regional volume (due to head movement) occur under the activation compared to rest condition, the measured activity will decrease which may lead to false-positive results. To illustrate the bias introduced by these approaches, we compared the original data with that obtained through re-analysis with anatomically-defined ROI and FBF realignment.

To obtain anatomically-defined striatal and cerebellar ROIs we used the criteria described by Mawlawi et al., (2001) to define dorsal and ventral striata on a magnetic resonance scan positioned in Montreal Neurological Institute (MNI) space. An [^{11}C]raclopride template was

constructed in MNI space (Meyer et al., 1999) using an average image of 8 scans obtained in healthy control subjects. This template was then spatially transformed into individual PET space and the resulting transformation parameters were used to transform the striatal ROI into individual space. We then combined analysis in re-defined ROIs with head movement correction using FBF-realignment. Non-attenuation corrected dynamic images were denoised using a level 2, order 64 Battle Lemarie wavelet (Battle 1987; Turkheimer et al., 1999). Frames were realigned to a single frame which had a high signal to noise ratio, using a mutual information algorithm (Studholme et al., 1996) and the transformation parameters were then applied to the corresponding attenuation corrected dynamic images. This procedure was applied to all frames to generate a FBF-corrected dynamic image.

Table 2 presents the regional BP values obtained in the original analysis (Koepp et al., 1998) and those obtained following ROI redefinition with subsequent FBF realignment. In the original study, repeated measures ANOVA revealed a significant effect of playing the video game ($F_{(1)}=7.72$; $p<0.01$), that was particularly marked in the ventral striatum (see Table 2). Following ROI redefinition, ANOVA showed only a trend-level effect of playing the video game ($F_{(1)} = 3.64$; $p=0.10$) and a significant effect of region ($F_{(3)}=90.98$; $p<0.01$). In common with our previous results, but of a smaller magnitude, post hoc t-tests did reveal a significant reduction in BP in the right ventral striatum during the video game condition ($t_{(7)}=4.94$; $p=0.01$; mean -7.3%), although this effect only reached trend level significance in the left ventral striatum ($t_{(7)}=2.10$; $p=0.07$; mean -4.7%). Whilst in our original data BP in all areas correlated with task performance (Koepp et al., 1998), when ROI were re-defined there were no correlations between performance and change in BP. Following ROI definition and FBF realignment, ANOVA showed a significant overall effect of condition ($F_{(1)} = 7.44$; $p=0.03$) and region ($F_{(3)} = 22.23$; $p=0.01$). However, the magnitudes of change were much smaller (see Table 2) and t-tests did not reveal any significant changes in individual dorsal or ventral striatal regions.

Although we did not observe significant changes in ROI size, or correlations between ROI size and performance during the scan, the diminished experimental effects observed when non-threshold ROI were used in the re-analysis suggests that head movement may have biased our published results. This conclusion is further strengthened by the observation that when FBF re-analysis was applied, the significance of magnitude of changes detected was further diminished. Thus, we cannot overstate the importance of appropriate head movement correction methods for analysis of task-induced DA release using [^{11}C]raclopride PET. Head movement correction is also of particular importance in studies of pharmacologically-evoked DA release when the pharmacological challenge may be associated with behavioral activation (e.g. amphetamine).

Maximizing detection sensitivity

As task-induced increases in DA release are likely to be relatively small and transient in nature, it is particularly important to maximize the sensitivity of these methodologies for detection of changes in DA release. As dual condition BI scans may offer advantage over paired bolus scans in minimizing the effects of changes in blood flow, the sensitivity of these approaches has been specifically compared: following administration of amphetamine (Carson et al., 1997) or nicotine (Marenco et al., 2004) to primates, bolus and BI approaches have roughly equivalent power to detect alterations in extracellular DA levels.

Dopamine kinetics and timing

A more important factor may be the shape and timing of the DA release curve in comparison to the radiotracer time-activity curve. Graphical analysis following bolus administration of [^{18}F]-N-methylspiroperidol showed that change in uptake rate is maximal for large DA

peaks and slow DA clearance (Logan et al., 1991). Similar results have been obtained for the dual condition, single scan BI approach; changes in specific binding following amphetamine challenge correlate with both the height of the DA pulse (nM) and the DA clearance rate (min^{-1}), and tightest correlations are obtained when the change in specific binding is correlated against the integral of the DA pulse ($\mu\text{M}\cdot\text{min}$) (Endres et al., 1997). It is unclear at present whether DA curves obtained under all physiological stimuli will be sufficient to produce significant radiotracer displacement using this technique.

Simulations performed by Morris and colleagues (1995) for the paired bolus approach suggest that BP changes may be maximized when the activation task is performed over a long time period, and commenced on or before radiotracer administration. Similar results were obtained by Logan et al., (1991), where the largest change in [18F]-N-methylspiroperidol uptake rate occurred when the task commenced simultaneously with radiotracer injection, a finding also replicated in [^{11}C]raclopride simulations of Endres et al., (1998). Yoder et al., (2004) have further demonstrated that the change in BP can be markedly affected by the timing of DA response in relation to the timing of [^{11}C]raclopride concentration following bolus administration, an interaction termed 'Effective Weighted Availability' (EWA). Here, greater changes in BP were detected if the onset of the DA response occurred just before [^{11}C]raclopride administration (Yoder et al., 2004). Furthermore, the magnitude of change in BP reflected not only the magnitude of DA release (area under the curve) but also differences in DA temporal kinetics (i.e. the gradient of the DA release curve), with blunt curves producing larger changes in BP for a given amount of DA released (Yoder et al., 2004). When using the paired bolus approach, it is therefore recommended that tasks start just prior to radiotracer administration and continue for a significant duration of the scan.

Pharmacological enhancement of dopamine release

An interesting strategy to increase detection of task-induced changes in DA release is the use of DA re-uptake inhibitors such as methylphenidate (MP), which has been used with some success (Volkow et al., 2002b; Volkow et al., 2004). As MP inhibits the re-uptake of released DA to the presynaptic terminal through dopamine transporters, released DA accumulates thus producing a greater magnitude of change in [^{11}C]raclopride binding (Volkow et al., 2002a). However, small but significant differences between four combinations of conditions (placebo or MP plus control or activation) are required in order for clear additive effects to be observed, meaning this approach has been difficult to validate; ideally dose-response studies of re-uptake inhibition are required. In addition, variable absorption of oral MP will introduce some noise into these measurements. Care is also required as DA reuptake inhibitors may also produce additional effects on regional blood flow, or on DA release via action on other neurotransmitter systems. Nonetheless, DA reuptake inhibition may theoretically be a useful 'pharmacological enhancement maneuver' for imaging task-induced DA release.

Voxel-based analysis

Differences in BP between control and activation conditions may also be determined using parametric analysis. Standard voxel-wise analysis can be carried out using statistical parametric mapping (SPM) software (Friston et al., 1995); (<http://www.fil.ion.ucl.ac.uk/spm/>). A further approach is the voxel-wise statistical method of Aston et al., (2000), currently available for data obtained using paired bolus scans. Different to the usual SPM approach, the method of Aston et al., (2000), uses residuals of the least squares fit of the kinetic model to estimate the standard deviation of BP measurements at each voxel from the noise of dynamic data. These standard deviations are then used to estimate the t statistic at each voxel and, in proportion to the number of time-frames in the dynamic data, the degrees

of freedom (df) are thereby greatly increased. Simulations showed that statistical sensitivity to detect changes in BP was greatly enhanced; indeed changes could be detected in single subjects across experimental conditions in simulated data (Aston et al., 2000). When considering what is currently known about the neuroanatomy of the striatum (see above), it would seem prudent that voxel-based approaches are presented alongside ROI-based analyses.

Measurement of extrastriatal DA release

Although the expression of $D_{2/3}$ receptors is highest in the striatum, dopaminergic projections from the dorsal midbrain show widespread efferents, additionally terminating in limbic, thalamic and cortical regions. DA acting within these regions is known, from research in experimental animals, to be important for diverse functions including stabilization of active representations relevant for working memory (Sawaguchi et al., 1991), episodic memory formation (Fujishiro et al., 2005; Umegaki et al., 2001) and affective-based learning (Baldi et al., 2007; de Oliveira et al., 2006; Pezze et al., 2004; Rosenkranz et al., 2002). There is some evidence in humans to suggest that DA manipulations using selective agents may influence similar functions (Cervenka et al., 2008; Gibbs et al., 2007; Mehta et al., 2005; Roesch-Ely et al., 2005), presumably mediated by changes in extrastriatal as well as striatal DA neurotransmission. The ability to reliably measure DA release in vivo in cortical and limbic regions outside the striatum would therefore enable the study of a broader range of functions modulated by DA neurotransmission, as well as investigation of potential interactions between extrastriatal and striatal DA systems (Pycock et al., 1980; Roberts et al., 1994).

To date, we are aware of three studies which have reported significant changes in extrastriatal [^{11}C]raclopride BP following non-pharmacological stimuli (Garraux et al., 2007; Kaasinen et al., 2004; Sawamoto et al., 2008). The critical question here is whether or not DA release can be accurately quantified outside the striatum using [^{11}C]raclopride (or other radiotracers - which will be discussed later). This question can be partly addressed by first asking whether measurement of [^{11}C]raclopride outside the striatum is valid, as the expression of $D_{2/3}$ receptors in extrastriatal regions is one to two degrees of magnitude lower than in the striatal areas (Camps et al., 1989; Hall et al., 1994). Early studies of [^{11}C]raclopride distribution in the brain following bolus administration showed that there was no obvious accumulation of [^{11}C]raclopride in cortical areas (Farde et al., 1987) and that [^{11}C]raclopride specific binding in cortical areas was only slightly higher than values obtained for the cerebellum and white matter (Farde et al., 1988). Furthermore, *ex vivo* autoradiography data obtained using [^3H]raclopride in human post-mortem brain tissue shows that specific binding in tissue taken from the frontal and temporal cortex is very low ($B_{\text{max}} < 0.7 \text{ pmol/g}$) compared to that in the striatum (caudate $B_{\text{max}} \sim 14.7 \text{ pmol/g}$) and that no specific binding is detected in tissue from the amygdala, cinguli, hippocampus or cerebellum (Hall et al., 1988).

More recently, this issue has been addressed by Hirvonen et al. (2003) using three analyses of [^{11}C]raclopride scans collected in eight individuals. First, test-retest reliability was quantified in the striatum, thalamus and temporal cortex. Using the putamen as a comparator, the thalamus showed good reliability based on the intraclass correlation coefficient (0.86) whereas the temporal cortex showed even better reliability (0.95). However, these calculations would have been affected by the higher between-subjects variability in these extrastriatal regions as indicated by the larger coefficients of variation. More telling is the range of within-subjects differences reported: the range increases from 16.87% in the putamen, to 26.03% in the thalamus and to 42.83% in the temporal cortex. Such marked variability is likely to influence the ability to detect BP differences following

administration of pharmacological agents (which either induce DA release, or occupy D_{2/3} receptors) or conduction of behavioral tasks. The authors concluded that for the thalamus “the signal-to-noise for quantification may become too low ... leading to an artifactual underestimation of measured D₂ receptor occupancy” (Hirvonen et al., 2003). We infer that this also applies to the cortical regions with even lower BP values. This is exemplified in data from two subjects in whom receptor occupancy with the non-selective DA receptor antagonist haloperidol was also measured. A dose of 0.5mg haloperidol gave similar occupancy values in the putamen and thalamus, whereas a higher dose (1.5mg) was paradoxically associated with markedly lower occupancy in the thalamus, in line with predictions from the analysis of noise contributions (Hirvonen et al., 2003). We have recently conducted a DA D_{2/3} receptor occupancy study using [¹¹C]raclopride and administration of 400mg sulpiride; striatal D_{2/3} occupancy following sulpiride administration is highly significant, but also very variable due to poor uptake of sulpiride into the brain (Mehta et al., 2008). As would be predicted by Hirvonen and colleagues (Hirvonen et al., 2003), we were able to detect D_{2/3} occupancy in the thalamus, but not the frontal cortex - indeed some subjects showed negative occupancy in this area (Pretorius et al., 2004), as illustrated in Figure 2.

A better approach, however, would be to compare [¹¹C]raclopride BP with BP measured using a radiotracer which allows better estimation of D_{2/3} receptor density in extrastriatal regions - such as [¹¹C]FLB457 and [¹⁸F]fallypride, which are very high (picomolar) affinity D_{2/3} receptor antagonists (Ito et al., 2008; Mukherjee et al., 1999; Olsson et al., 1999). Ito et al. (2008) measured regional binding potentials acquired in the same volunteers using both [¹¹C]raclopride and [¹¹C]FLB457. These data allow direct comparison of BP estimations in extrastriatal regions to be made using correlational analysis. We have performed this analysis using the data reported in the manuscript, and a strong positive relationship between the regional values across both tracers is apparent. However, this correlation is heavily influenced by the large striatal signals obtained for both radiotracers - importantly, there is no correlation between [¹¹C]FLB457 and [¹¹C]raclopride BP ($r_s=0.032$; $p=0.92$) when striatal regions are removed from the analysis (see Figure 3). These data demonstrate that the inferior signal to noise ratio of [¹¹C]raclopride in extrastriatal areas leads to poor quantification of DA D₂ receptor availability when compared to the signal from a tracer specifically designed to quantify binding in such regions. While the correlation coefficient was close to zero and the number of volunteers in this study was typical of PET receptor studies ($n=10$) it would be important for this finding to be confirmed in a larger cohort and to be tested across individual brain regions including the thalamus and cortical regions.

Despite these concerns surrounding the validity of measurement of extrastriatal D_{2/3} receptors with [¹¹C]raclopride, it remains possible to calculate signal changes in these regions and some authors have applied these calculations to the study of extrastriatal DA release with cognitive tasks, with some positive findings to date (Garraux et al., 2007; Sawamoto et al., 2008). A whole-brain, voxel-wise analysis of our recent findings of striatal DA release during a planning task (Lappin et al., 2009) also reveals changes in [¹¹C]raclopride BP in extrastriatal regions (see Figure 4A). Statistically significant changes can be seen in a number of regions, most notably the anterior cingulate cortex. The figure also shows reduction in [¹¹C]raclopride BP during planning in the region of the substantia nigra (left) and possibly the pituitary gland. One concern is that the BP values may be poorly quantified and indeed one subject had negative BP values in the anterior cingulate cortex. Significant changes were still present upon removing this outlier.

In light of the doubts regarding accurate estimation of low BP values as discussed above it is difficult to confidently attribute these apparent effects to changes in endogenous DA levels. This is compounded by the absence of clear experimental evidence relating actual DA

release to changes in [^{11}C]raclopride binding in extrastriatal regions. Nonetheless, close inspection of the BP curves (as shown in Figure 4B) for the anterior cingulate cortex during planning and rest show a separation of the signal across the entire experiment including the early frames acquired during tracer uptake where no differences in striatal BP values were observed. Again, these factors make it difficult for us to attribute the later changes to DA release. But what of the findings in the previous published studies? Here, we believe we must also be cautious for the same reasons, and due to additional statistical concerns. While we have noted changes that survive multiple comparisons correction across the whole brain volume, both Sawamoto et al., (2008) and Garraux et al., (2007) utilized ROI analyses (of areas within the anterior cingulate and caudal frontal cortex respectively), in order to limit the multiple comparisons correction required. This is, of course, an acceptable approach provided that the regions of interest are defined independently of the analysis reported. It is unclear for either of these studies whether this was the case. Indeed Garraux et al. (2008) explicitly state that multiple comparisons correction was conducted using a '5-mm-radius spherical volume centered on the peak' (page 14438).

An interesting caveat with regards to measurement of extrastriatal DA release measured with [^{11}C]raclopride may be the ventral tegmentum and substantia nigra. Within these regions $\text{D}_{2/3}$ receptors are highly expressed, although not present on all projecting dopaminergic neurons (Lammel et al., 2008). However, the size of the midbrain dopaminergic nuclei relative to the typical resolution may compromise detection of DA release in this region. For example the size of the ventral tegmental area ($\sim 60\text{mm}^3$) would be of the same order of magnitude as a single voxel when the voxel size is approximately $4\times 4\times 4\text{ mm}$. The substantia nigra may therefore contribute more to any midbrain signals seen, although without high quality localization of this region and partial volume correction any findings in these regions must be treated with caution. Thus, it is interesting to note that for our voxel-wise analysis of the planning task shown in Figure 4A (conducted without partial volume correction), significant BP change was observed in the region of the substantia nigra. We have also shown measurable receptor occupancy with 400mg sulpiride in the same region bilaterally, of the same degree as that seen in the striatum (Mehta et al., 2008).

In conclusion, it is clear that measurable signal in some extrastriatal regions is present for [^{11}C]raclopride scans and that changes in BP can be calculated in the same regions relating to drug administration or task performance. However, the work of Hirvonen et al. (2003) and the analyses of receptor occupancy and re-analysis of Ito et al. (2008) presented here strongly question the validity of accurate quantification of cortical signal changes of [^{11}C]raclopride BP.

Recent data suggest that extrastriatal [^{11}C]FLB457 and [^{18}F]fallypride binding may also be sensitive to competition with endogenous DA in man (Aalto et al., 2005; Christian et al., 2006; Cropley et al., 2008; Ko et al., 2009; Montgomery et al., 2007; Narendran et al., 2009; Riccardi et al., 2006a; Riccardi et al., 2006b; Slifstein et al., 2004). Of these radiotracers, recent data indicates that [^{11}C]FLB457 may be more sensitive than [^{18}F]fallypride in detecting increases in cortical DA release due to a higher signal to noise ratio (Narendran et al., 2009), and that the sensitivity of [^{18}F]fallypride in measuring decreases in extracellular DA levels may be limited (Cropley et al., 2008). While further confirmation is required, these radiotracers may present the important opportunity to examine relationships between cortical DA release and cognitive function. To date, we are aware of three studies that have adopted this approach to measuring task-induced increases in extrastriatal DA release (Aalto et al., 2005; Christian et al., 2006; Ko et al., 2009). Using [^{18}F]fallypride and the LSSRM model of Alpert et al., (2003), Christian et al., (2006) detected a significant increase in [^{18}F]fallypride displacement in the thalamus as subjects performed a spatial attention task,

and this increase in displacement was highly correlated with task performance. Using [^{11}C]FLB457, Aalto et al., (2006) observed decreases in binding in the ventral anterior cingulate cortex during both a verbal working memory and a sustained attention task. Furthermore, in the ventrolateral frontal cortex and left medial temporal structures, [^{11}C]FLB457 BP was lower during the verbal working memory task than during the sustained attention task (Aalto et al., 2005). Again using [^{11}C]FLB457, Ko et al., (2009) have recently reported increases in DA release in the right dorsal anterior cingulate cortex during a card sorting test of cognitive flexibility, compared to a control task, indicating a role for prefrontal cortical DA in cognitive flexibility in man, in accordance with findings from animal research (Floresco et al., 2006). These results suggest that it may be possible to associate behavioral performance with DA release in extrastriatal as well as striatal brain areas using select tracers, allowing the role of frontal dopamine function in human cognition to be further explored.

Dopamine release during non-pharmacological paradigms

Returning to striatal DA release, we now review the findings reported in published studies of DA release following non-pharmacological stimuli. Whilst the published studies should be carefully considered with respect to the methodological factors outlined above, significant decreases in $\text{D}_{2/3}$ radiotracer binding have been detected in many studies, as summarized in Table 3. Research on DA release has centered on four main areas into which the literature cited in Table 3 is organized: motor performance and sequential learning; reward-related processes; psychological and pain stress; and cognitive tasks and states. As can be seen by quick inspection of this table, for several of these modalities increased DA release is reported using different paradigms and radiotracer methodologies, often in studies performed at different research centers. Many behavioral tasks will include more than one of these component processes that may individually contribute to DA release – for example, motor responses are often required during behavioral tasks designed to assess cognitive performance. Although correlations between change in BP and the specific behavioral measures of interest can be explored, recent years have seen a growing trend towards the more refined approach of including a control scan, in which measures not under specific investigation (for example, motor output) are matched to the test condition.

Motor performance and sequential motor learning

Several studies have shown that $\text{D}_{2/3}$ radiotracer BP in the dorsal striatum decreases when subjects perform repetitive limb movements during the scan; paradigms include a hand-writing task, foot extension/flexion and simple finger movements (Badgaiyan et al., 2003; Goerendt et al., 2003; Lappin et al., 2008; Lappin et al., 2009; Larisch et al., 1999; Ouchi et al., 2002; Schommartz et al., 2000). These decreases in BP have been reported following [^{123}I]IBZM SPET (Larisch et al., 1999; Schommartz et al., 2000), paired bolus [^{11}C]raclopride PET (Goerendt et al., 2003; Lappin et al., 2009; Ouchi et al., 2002) or [^{11}C]raclopride bolus displacement (Badgaiyan et al., 2003) methodologies. The only study to report negative results administered [^{11}C]raclopride after completion of a motor task (treadmill running) (Wang et al., 2000), suggesting that there may be a requirement for ongoing DA release in the presence of the radiotracer in order for significant effects to be observed. The positive study of Schommartz et al., (2000) was the first study of task-induced DA release to employ a non-resting control condition; [^{123}I]IBZM binding in a handwriting task was compared to that in a reading task, thought to involve an equivalent cognitive load but without the motor requirements. As detailed in Table 3, this approach has since been adopted in a number of studies.

Some evidence suggests that DA release may also mediate motor learning. Widespread reductions in striatal [^{11}C]raclopride binding have recently been reported during a finger

sequence learning task using a single bolus plus constant infusion paradigm (Garraux et al., 2007), although as the control condition was not matched for motor output, DA release associated with motor learning could not be dissociated from that associated with motor performance. Use of motor control conditions to investigate changes in DA which may specifically relate to motor learning have been employed in two studies by Badgaiyan and colleagues (Badgaiyan et al., 2007; Badgaiyan et al., 2008). Here, both implicit and explicit learning of complex motor sequences, relative to a motor control condition, increased [^{11}C]raclopride displacement in the caudate and putamen (Badgaiyan et al., 2007; Badgaiyan et al., 2008). However, as these studies used a [^{11}C]raclopride single bolus displacement paradigm, confounding effects of blood flow changes cannot be excluded (see above). We have recently compared DA release during motor sequence learning and motor sequence execution within subjects using paired bolus [^{11}C]raclopride scans (Lappin et al., 2009), and did not find any significant differences in [^{11}C]raclopride between sequence learning and execution, although both conditions significantly decreased [^{11}C]raclopride binding in the sensorimotor and associative striatum compared to resting baseline values. This result therefore questions the extent to which motor and cognitive tasks components may be separated in terms of DA release in striatal subdivisions.

Reward-related processes

^{11}C -raclopride PET studies have investigated the role of striatal DA in several aspects of reward in humans. With respect to reward consumption, Small et al., 2003 have shown that decreases in [^{11}C]raclopride BP occur in the dorsal caudate and dorsal putamen, following consumption of a 'favorite meal' just prior to scanning (Small et al., 2003). In this study, the feeding-induced decreases in [^{11}C]raclopride BP, which were observed in previously food-deprived subjects, were correlated with subjective ratings of pleasantness, hunger and satiety.

Studies in experimental animals reveal that the relationship between reward and striatal DA levels is complex. Whilst microdialysis studies demonstrate that lever pressing for natural reinforcers, such as food, increases striatal DA release (e.g. Hernandez et al., 1988), further research indicates that it is the requirement for operant responding (lever pressing), rather than the presence of the reward itself, which is associated with increased DA (Salamone et al., 1994; Sokolowski et al., 1998). This is mirrored in human studies of DA release; decreased striatal ^{11}C -raclopride BP is observed during an active (Zald et al., 2004) but not a passive (Hakymez et al., 2007) reward task. Decreases in [^{11}C]raclopride BP in the ventral and dorsal striatum have also recently been detected in Parkinsonian patients during a gambling task requiring active responses (Steeves et al., 2009). Interestingly, in the ventral striatum, the change in [^{11}C]raclopride BP was greater in patients with a pathological gambling disorder than control patients, whilst baseline D2/3 receptor availability was lower (Steeves et al., 2009). This is accordant with animal research suggesting that low D2/3 receptor availability may mediate vulnerability to addiction (Dalley et al., 2007), and that aspects of addiction may be mediated through sensitized DA release (Robinson and Berridge, 2000; Volkow et al., 2006).

In animals, as a cue becomes paired with a reward during Pavlovian conditioning, increases in DA neuron firing rate become more tuned to the reward-predicting cue than to the reward itself (Schultz 1998), so that increases in striatal DA release occur on cue presentation (Kiyatkin et al., 1996; Phillips et al., 2003). Recently, cue-induced DA release has been investigated using a delayed monetary incentive task (Schott et al., 2008). In comparison to a neutral control condition (designed to minimize sensorimotor and cognitive differences between conditions), decreases in [^{11}C]raclopride BP were observed in the left ventral striatum (nucleus accumbens). Volkow et al., (Volkow et al., 2002b; Volkow et al., 2006) have investigated cue-induced DA release in food-deprived or cocaine-addicted volunteers.

In food-deprived subjects, food-associated cues did not significantly alter [^{11}C]raclopride BP in the striatum, except when combined with methylphenidate (Volkow et al., 2002b). However, in cocaine-addicted volunteers, drug-associated cues delivered via a video of the simulated purchase, preparation and smoking of crack cocaine produced significant decreases in dorsal striatal [^{11}C]raclopride BP. These changes correlated with self-reports of craving and may relate to habitual aspects of compulsive drug taking (Volkow et al., 2006). Together, these results are consistent with the hypothesis that reward anticipation and reinforcement learning may relate to DA responses in the ventral striatum, but that DA process linked to habitual behaviors in addiction are mediated by more dorsal striatal regions (Porrino et al., 2004).

There is some evidence that, in clinical disorders, drug placebos can also act as reward-predicting cues, in that placebo administration may lead to expectation of clinical benefits, such as pain relief, which function as rewards (de la Fuente-Fernandez et al., 2004). Placebo-induced DA release across the striatum has been observed in Parkinson's Disease patients following administration of saline in place of apomorphine (de la Fuente-Fernandez et al., 2001; de la Fuente-Fernandez et al., 2002) and during sham rTMS (Strafella et al., 2006). In the apomorphine study, the change in [^{11}C]raclopride binding in the dorsal striatum correlated with the amount of clinical benefit reported following placebo administration (de la Fuente-Fernandez et al., 2001; de la Fuente-Fernandez et al., 2002; de la Fuente-Fernandez et al., 2004) and a similar but non-significant trend was observed following rTMS (Strafella et al., 2006). Although only observed using voxel-wise and not ROI analysis, a similar result in the ventral striatum has recently been suggested following administration of a placebo for glucose in fasted men (Haltia et al., 2008). These studies, performed by different groups, both utilized paired bolus scans. Increased extracellular DA in the striatum in response to placebo administration has also been observed in analgesia studies using BI methodology; [^{11}C]raclopride BP decreased in the placebo condition both during the expectation of pain (Scott et al., 2007a), and during the delivery of the painful stimulus (Scott et al., 2008). Here, the DA release in the ventral striatum appeared to be particularly associated with the placebo response (Scott et al., 2007a; Scott et al., 2008). Decreased [^{11}C]raclopride BP may also be particularly apparent in the ventral striatum when placebo tablets are administered in place of psychostimulant drugs; when placebo tablets, identical to the previously administered amphetamine tablets, were given in an environmental setting previously paired with amphetamine administration, marked decreases in [^{11}C]raclopride binding in the ventral striatum were detected (23%) (Boileau et al., 2007).

In the novel [^{11}C]raclopride displacement method of Pappata et al., (2002,) significant [^{11}C]raclopride displacement in the ventral striatum occurred in an unexpected monetary gain condition (Pappata et al., 2002). Using a carefully designed study with an appropriate sensorimotor control condition and an established [^{11}C]raclopride modeling technique, it has been demonstrated that unpredictable monetary rewards increase DA levels in the medial left caudate nucleus (Zald et al., 2004). As stated above, in accordance with microdialysis studies of operant responding in animals (Salamone et al., 1994), this increase in DA appears dependent on the requirement for subjects to make a behavioral response, as no increase in DA was seen during a passive reward task (Hakymez et al., 2008). Interestingly, during both active and passive reward tasks, increases in [^{11}C]raclopride binding were detected in the putamen, indicating decreases in DA release, possibly due to withholding of expected rewards (Hakymez et al., 2008; Zald et al., 2004). Similarly, when alcohol predicting cues were presented whilst subjects were in the scanner, but alcohol was not given until after the scan had finished, increases in [^{11}C]raclopride binding were observed in the right ventral striatum (Yoder et al., 2009). Increases in [^{11}C]raclopride binding have also been observed in the dorsal striatum of fasted men administered placebo for glucose (Haltia et al., 2008). Although unclear at present, these results may relate to decreases in DA

neuronal firing which have been observed in animals when expected rewards are omitted ('negative prediction error') (Schultz, 1997; Schultz, 1998) and an altered balance between the potentially opposing effects (Grace, 1991) of phasic DA release and the level of tonic (population) dopaminergic activity on [^{11}C]raclopride binding (Hakymez et al., 2008). Whilst interesting, substantial work in experimental animals investigating changes in striatal [^{11}C]raclopride binding in relation to tonic and phasic DA neuron firing, and under different reward paradigms in awake animals (Patel et al., 2008), is required before these effects can be clearly interpreted.

The animal literature on DA release in reward and reinforcement presents a complex picture, and the precise role of DA in different divisions of the striatum in reward and reinforcement learning is still under debate (Salamone 2007). Whilst these PET studies provide compelling evidence for DA release in the human striatum across several reward paradigms, the direction, magnitude and regional selectivity of these responses likely depends on factors such as reward / reinforcement contingencies and predictability, conditioning and habit formation, as is the case in the animal literature.

Psychological and pain stress

In animals, cortical and striatal DA release increases following exposure to stressors such as chronic restraint, foot or tail-shock (Abercrombie et al., 1989; Imperato et al., 1991; Sorg et al., 1991). Stress is believed to be an important factor in the development of disorders such as schizophrenia and depression, and this association may be mediated by molecular alterations in DA systems (Butzlaff et al., 1998; Howes et al., 2004; Thompson et al., 2004; Walker et al., 1997). The striatal DA response to stress using [^{11}C]raclopride PET has been investigated using arithmetic tasks as psychological stressors (Montgomery et al., 2006a; Pruessner et al., 2004; Soliman et al., 2008), and pain stress (Scott et al., 2006; Scott et al., 2007b). The experimental design employed in two studies by the same group (Pruessner et al., 2004; Soliman et al., 2008) used an arithmetic task which was performed in-front of a study investigator, who regularly gave negative verbal feedback. This design is thought to particularly induce psychosocial stress. In the stress condition decreases in [^{11}C]raclopride binding were apparent and these were particularly notable in the ventral striatum. Interestingly, the decreases in [^{11}C]raclopride binding were only apparent in vulnerable individuals (those reporting low maternal care or scoring highly on a negative schizotypy scale). Under a different arithmetic task, but relative to a matched control condition and using dual condition BI [^{11}C]raclopride administration, we were unable to detect any stress-induced DA release (Montgomery et al., 2006a). This difference may be because the task may not have loaded quite so highly on psychosocial stress, or may relate to the fact that only a small proportion of these volunteers reported low maternal care. In similarity to this, the bolus study of Volkow et al., (2004), performed in individuals who were not selected on the basis of stress vulnerability, showed no difference in [^{11}C]raclopride binding during an arithmetic task, except in the presence of methylphenidate. Therefore, the vulnerability of the subjects, and the degree to which tasks load on psychosocial stress (in addition to the cognitive challenge of the arithmetic task) may be important in eliciting DA release.

The use of painful stimuli as stressors may cause a large DA response. Using BI methodology, large decreases in [^{11}C]raclopride BP occurred across the striatum on administration of hypertonic saline to the masseter muscle (Scott et al., 2006; Scott et al., 2007b). Interestingly, whilst changes in dorsal striatal areas were particularly associated with pain ratings, those in the ventral striatum correlated with a negative affective state and fear ratings (Scott et al., 2006). These data indicate that striatal DA release in the human brain may occur in response to aversive (Scott et al., 2006; Scott et al., 2007b) as well as rewarding (Hakymez et al., 2008; Small et al., 2003; Volkow et al., 2006; Zald et al., 2004) stimuli.

Cognitive tasks and states

Functional MRI and rCBF studies reveal striatal activation during performance of several cognitive tasks, including spatial planning, spatial working memory and set-shifting (Dagher et al., 1999; Mehta et al., 2003; Monchi et al., 2001; Monchi et al., 2006b; Owen et al., 1996; Owen 2004; Rogers et al., 2000). Although less work has been performed in this area, dopaminergic contributions to some aspects of cognitive functioning have been investigated using PET. In particular, decreases in [^{11}C]raclopride BP were observed when planning a set shift (Monchi et al., 2006a), and during spatial planning (Lappin et al., 2009) and spatial working memory tasks (Sawamoto et al., 2008). Whilst decreases in [^{11}C]raclopride BP were detected compared to non-resting control conditions in the investigations of Monchi et al., 2006a and Sawamoto et al., 2008; in the spatial planning investigation of Lappin et al., (2009) the cognitive components of the task could not be clearly separated from motor components. Interesting, the results from all these studies suggest that effects may be greatest in the caudate, which would be in accordance with predictions from striatal anatomy (Alexander et al., 1986; Haber et al., 2000) and the functional subdivision model (Martinez et al., 2003) which suggest that DA in the caudate (associative striatum) may particularly modulate cognitive functions.

Finally, some evidence suggests that [^{11}C]raclopride BP values may also vary according to the internal cognitive state of the individual when no behavioral output is required. Yoga-Nidra meditation is associated with decreases in BP in the ventral striatum (Kjaer et al., 2002) and a small study suggested volunteer uncertainty of the experimental procedure (whether or not alcohol would be infused) also alters baseline BP (Yoder et al., 2008). Whilst further confirmation is required, this latter study, together with those of psychological stress in vulnerable individuals (Pruessner et al., 2004; Soliman et al., 2008) may illustrate the importance of carefully controlled experimental conditions during PET investigations of DA release.

Conclusions

These studies demonstrate that increases in DA release can be observed in the human striatum during performance of several behaviors to which a central role of DA has been ascribed from studies performed in experimental animals. Further credence to these findings is provided through the observation that decreases in [^{11}C]raclopride BP or displacement have been repeatedly reported during motor, reward-related and cognitive tasks using an array of methodologies. Nonetheless, imaging task-induced DA release is also associated with significant potential for experimental bias, which may originate from a number of sources, including increases in head movement or changes in rCBF during the task condition. The relative sensitivity of the different methodological approaches to potential bias will be balanced against practical considerations when performing studies of this type and hence optimal experimental design may vary according to the hypothesis under investigation.

Although some association between regional changes in BP and discrete elements of task performance has been achieved using either correlational analysis or subtraction methods, further work using carefully designed control conditions is required to determine the extent to which these processes may be dissociated at the regional and functional level. The distribution of $\text{D}_{2/3}$ receptors and characteristics of available $\text{D}_{2/3}$ radiotracers dictates that, at present, confident detection of task-induced changes in extracellular DA levels is principally limited to the striatum. Although some encouraging results in extrastriatal regions have been reported using high-affinity $\text{D}_{2/3}$ antagonist radiotracers (Aalto et al., 2005; Christian et al., 2006), further confirmation of the sensitivity of these radiotracers to extrastriatal alterations in DA is required.

To date, the majority of investigations into the dopaminergic basis of human behavior have been performed in healthy volunteers. A significant challenge for future research lies in the determination of associations between behavioral and cognitive symptoms of psychiatric and neurological disorders and aberrant DA release whilst performing relevant tasks. As the changes in BP that are detected are reasonably small, between-group comparisons are challenging and use of enhancement methodologies such as inhibition of DA reuptake may be particularly useful in this setting. Increased understanding of the links between abnormal DA release and the symptoms and progression of disorders such as schizophrenia, Parkinson's disease and addiction may have important implications for clinical and therapeutic intervention strategies.

Acknowledgments

The authors would like to thank Prof. Alain Dagher (Montreal Neurological Institute, McGill University, Montreal, Canada) and Dr Stephanie Cragg (University of Oxford, UK) for their valuable input to this manuscript.

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Figure 1. Regional cerebral blood flow during performance of a videogame

Four healthy male volunteers each underwent a 12 run quantitative H₂-[15]O PET study. The volunteers were at rest during runs 1-5 and 11-12 and were playing a videogame during runs 6-10. **A** presents rCBF values for the dorsal and ventral striatum and cerebellum. The videogame was associated with increases in rCBF in all ROI, but to the greatest extent in the cerebellum. In **B**, data is presented as rCBF values in dorsal and ventral striatal ROI divided by rCBF values obtained in the cerebellum to provide 'R1' values. Here, decreases in 'R1' are apparent in striatal ROIs during the videogame.

Figure 2. Occupancy of the D2/3 receptors in different brain regions following administration of 400mg sulpiride

Seven healthy male volunteers (28-54 years, 65-85 kg) were administered either placebo or 400 mg of sulpiride. The subjects were dosed 90 min prior to the bolus injection of [^{11}C]raclopride followed by a continuous infusion ($\text{Kbol}=105$ min, 170-340 MBq at start of scan). The 80-minute PET studies were performed on a CTI ECAT EXACT 3D tomograph offering a spatial resolution of $4.8 \text{ mm} \times 4.8 \text{ mm} \times 5.6 \text{ mm}$ and an axial FOV of 23.4 cm. The dynamic PET images were realigned using FBF realignment after wavelet denoising. Each dynamic PET scan was summed for the equilibrium period (35 to 80 minutes) and was normalised to a [^{11}C]raclopride PET template in MNI space. A probabilistic atlas (Hammers et al., 2003), also in MNI space, was placed over each normalised integrated PET images to generate the radioactivity concentration at equilibrium in the reference (Creference) and target (Ctarget) regions. The regional BP values were estimated using, $\text{BP} = ((\text{Ctarget} - \text{Creference}) / \text{Creference})$ for both the placebo and sulpiride conditions. The regional occupancy values of the D2/3 receptors by sulpiride were calculated from the BP values as $\text{Occupancy} = ((\text{BP}_{\text{placebo}} - \text{BP}_{\text{drug}}) / \text{BP}_{\text{placebo}}) \times 100$. Data is presented for seven subjects (shown as different coloured symbols) as the mean occupancy per region for all subjects ($\pm$ standard deviation). Using a one-tailed paired t-test, the drug BP values were statistically lower from the placebo BP values in the striatal ($p < 0.001$) and thalamic ($p < 0.02$) regions, but not cortical areas ($p > 0.05$). Due to the high degree of variance across subjects in cortical BP values, the mean occupancy in the cortical areas could not be estimated reliably. In addition, some subjects showed negative occupancy in extrastriatal areas. This data has previously been presented in abstract form (Pretorius et al., 2004).

Figure 3. Scatterplot of extrastriatal binding potentials measured using two different dopamine D2 radiotracers ([11C]-raclopride and [11C]-FLB457) in the same 10 volunteers from Ito et al., (2008)

The plot was obtained using data presented in Ito et al. (2008). Correlational analysis shows that there is no significant relationship between ([11C]-raclopride and [11C]-FLB457 extrastriatal binding potentials ($r_s=0.032$; $p=0.92$).

Figure 4. Change in extrastriatal [11C]-raclopride BP during a Tower of London planning task
A: BP values are presented in the planning task compared to rest, overlaid on a T1-weighted MRI image, analysed with SPM5. All clusters are significant at $p < 0.05$ after correction for multiple comparisons across the entire volume, with a voxel height threshold of $p < 0.001$. Sagittal section is at $x=8$, transverse section at $y=-10$. Statistically significant changes can be seen in the anterior cingulate cortex (ACG), in the region of the substantia nigra (left) and possibly the pituitary gland. **B:** An ROI was extracted around the significant cluster in the ACG and used to extract time-activity curves from individual scan data. Data is presented as mean $\pm$ standard deviation and the striatum (STR) is included for comparison. During the equilibrium sampling period (35-75 minutes), BP was significantly lower in the task condition in both the STR ($p < 0.05$) and ACG ($p < 0.01$). However, in the ACG but not the STR a separation in signal is apparent across the entire experiment. In addition, a high level of noise was associated with ACG BP measures. Experimental details are provided in Lappin et al., (2008).

Table 1
Non-pharmacological studies of dopamine release in man: Methodological aspects

Non-pharmacological studies of dopamine release are presented according to publication date in order to highlight the development of applied methodologies.

Task/ Stimulus	Tracer	Subjects	Infusion	Scans	BP derivation	Analysis	Head movement reduction/ correction	Reference
Video game	[11C]Raclopride	8	B	2	SRTM	ROI (threshold)	Head rest	Koepp et al., 1998
Writing	123I-IBZM	8 (MM); 18 (MM)	B	1 (bs)	Ratio	ROI (SPET)	None specified	Larisch et al., 1999
After running	[11C]Raclopride	12 (HV)	B	2	Ratio	ROI (PET)	Head rest	Wang et al., 2000
Writing	123I-IBZM	8 (HV) 8 (HV)	B	1 (bs)	Ratio	ROI (SPET)	None specified	Schomartz et al., 2000
Placebo	[11C]Raclopride	12 (PD)	B	3	GA	ROI (PET)	Restraint (mask) PET-PET registration ⁹	De la Fuente-Fernandez et al., 2001, 2002
rTMS (dIPFC)	[11C]Raclopride	8 (HV)	B	2	SRTM	ROI (MRI) Voxel-wise ²	PET-MRI registration ⁷	Strafella et al., 2001
Meditation	[11C]Raclopride	8 (HV)	B	2	SRTM	ROI (MRI)	None specified	Kjaer et al., 2002
Foot movement	[11C]Raclopride	8 (HV) 8 (PD)	B	1-2	GA	ROI (MRI) Voxel-wise ¹	Restraint (mask)	Ouchi et al., 2002
Food stimulus	[11C]Raclopride	10 (HV)	B	4	GA	ROI (PET)	None specified	Volkow et al., 2002
Reward	[11C]Raclopride	12 (HV)	B	1	Novel method	ROI (threshold) Template ⁴ Voxel-wise	Restraint (mask) PET-PET registration ⁸	Pappata et al., 2002
Motor sequence execution	[11C]Raclopride	8 (HV) 6 (PD)	B	2	SRTM	ROI (MRI/PET) Voxel-wise ¹	Restraint (strap)	Goerendt et al., 2003
HFS of STN	[11C]Raclopride	6 (PD)	B	2	SRTM	ROI (MRI) Voxel-wise ²	PET-MRI registration ⁷	Strafella et al., 2003a
Finger Opposition	[11C]Raclopride	6 (HV)	B	1	LSRRM	Voxel-wise ³	PET-PET registration	Badgaiyan et al., 2003
Food	[11C]Raclopride	7 (HV)	B	2	SRTM	ROI (MRI) Voxel-wise ²	PET-MRI registration ⁷	Small et al., 2003
rTMS (MC)	[11C]Raclopride	6 (HV)	B	2	SRTM	Voxel-wise ²	PET-MRI registration ⁷	Strafella et al., 2003b

Task/ Stimulus	Tracer	Subjects	Infusion	Scans	BP derivation	Analysis	Head movement reduction/ correction	Reference
Arithmetic task	[11C]Raclopride	5 (HV _{ip}) 5 (HV _{np})	B	2	SRTM	ROI (MRI) Voxel-wise ²	PET-MRI registration ⁷	Preussner et al., 2004
Placebo	[11C]Raclopride	8 (HV)	B	2	SRTM	ROI (PET) Template ⁴ Voxel-wise ¹	Head rest PET-PET registration ⁸	Kaasinen et al., 2004
Variable ratio reward schedule	[11C]Raclopride	10 (HV)	B	3	SRTM	Voxel-wise ²	PET-MRI registration ⁷ Realignment algorithm ¹⁰	Zald et al., 2004
Arithmetic task	[11C]Raclopride	16 (HV)	B	4	GA	ROI (PET)	None specified	Volkow et al., 2004
Limb stimulation	[11C]Raclopride	8 (HV)	B	2	STRM	ROI (PET)	None specified	Thobios et al., 2004
rTMS (MC)	[11C]Raclopride	7 (PD)	B	2	SRTM	ROI (MRI) Voxel-wise ²	PET-MRI registration ⁷	Strafella et al., 2005
Placebo rTMS (MC)	[11C]Raclopride	7 (PD)	B	2	SRTM	ROI (peak) Voxel-wise ²	PET-MRI registration ⁷	Strafella et al., 2006
Arithmetic task	[11C]Raclopride	14 (HV)	BI	1	Ratio	ROI (MRI) ⁵ Template ⁴ Voxel-wise	PET-PET registration ⁹ with wavelet denoising ¹¹ (non-att)	Montgomery et al., 2006
rTMS (dlPFC)	[11C]Raclopride	9 (D) 14 (HV)	B	2	SRTM	ROI (MRI)	None specified	Kuroda et al., 2006
Conditioned stimuli	[11C]Raclopride	18 (CA)	B	2	GA	ROI (PET) Voxel-wise ¹	None specified	Volkow et al., 2006
Pain stress	[11C]Raclopride	8 (HV) 17 (HV)	BI	2 1(2)	Ratio Ratio/GA	Voxel-wise ¹	Light restraint PET-PET registration ¹²	Scott et al., 2006
Executive function	[11C]Raclopride	6 (HV)	B	2	SRTM	Voxel-wise ²	PET-MRI registration	Monchi et al., 2006
Conditioned stimulus	[11C]Raclopride	9 (HV)	B	3	SRTM	ROI (MRI) Voxel-wise ³	PET-PET registration ¹³	Boileau et al., 2007
Pain stress	[11C]Raclopride	4 (HV)	BI	2(2)	Ratio/GA	Voxel-wise ¹	Light restraint PET-PET registration ¹²	Scott et al., 2007a
Placebo	[11C]Raclopride	14 (HV)	BI	2	Ratio/GA	Template ⁶ ROI	Light restraint PET-PET registration ¹²	Scott et al., 2007b

Task/ Stimulus	Tracer	Subjects	Infusion	Scans	BP derivation	Analysis	Head movement reduction/ correction	Reference
Motor sequence learning	[11C]Raclopride	8 (HV)	B	1	LSSRM	Voxel-wise ³	Restraint (pillow) FBF (PET-PET)	Badgaiyan et al., 2007
Motor sequence learning	[11C]Raclopride	15 (HV)	BI	1(2)	Ratio	Template ⁴ ROI (MRI) ⁵ Voxel-wise ¹	Restraint (mask) PET-PET registration	Garraux et al., 2007
Uncertainty	[11C]Raclopride	13 (HV)	B	1 (bs)	GA	ROI (MRI) Voxel-wise	PET-PET registration	Yoder et al., 2008
Motor memory	[11C]Raclopride	7 (HV _e)	BI	2	Ratio	ROI (MRI) ⁵	PET-MRI registration ⁷ with wavelet denoising ¹¹	Floel et al., 2008
Passive reward	[11C]Raclopride	12 (HV)	B	3	SRTM	ROI (MRI) ⁶ Voxel-wise ²	Realignment algorithm ¹⁰	Hakymez et al., 2008
Placebo	[11C]Raclopride	20 (HV)	BI	2	Ratio/GA	Voxel-wise ¹	Light restraint PET-PET registration ¹²	Scott et al., 2008
Explicit motor memory	[11C]Raclopride	6 (HV)	B	1	LSSRM	Voxel-wise ³	PET-PET registration	Badgaiyan et al. 2008
Arithmetic task	[11C]Raclopride	10 (HV) 9 (HV _{PerAb}) 7 (HV _{PDysAd})	B	2	SRTM	ROI Voxel-wise ²	PET-MRI registration ⁷ realignment algorithm ¹⁰	Soliman et al., 2008
Spatial working memory	[11C]Raclopride	7 (HV) 7 (PD)	B	2	SRTM	ROI (MRI) ⁵ Voxel-wise ⁵	Restraint (strap) Polaris system ¹⁴	Sawamoto et al., 2008
Spatial planning	[11C]Raclopride	10 (HV)	BI	3	Ratio	ROI (MRI) ⁶ Template ⁴ Voxel-wise ¹	PET-PET registration ⁹ with wavelet denoising ¹¹ (non-at)	Lappin et al., 2008
Placebo	[11C]Raclopride	12 (HV) 12 (O)	B	2	STRM	ROI (MRI) Voxel-wise	PET-PET registration ⁸	Haltia et al., 2008
Reward	[11C]Raclopride	11 (HV)	B	2	GA	ROI (MRI) Voxel-wise	PET-MRI registration ¹⁵	Schott et al., 2008
Alcohol cue	[11C]Raclopride	8 (HV)	B	3	GA	Voxel-wise ¹	PET-MRI registration	Yoder et al., 2009
Gambling task	[11C]Raclopride	7 (PD) 7 (PDpg)	B	2	STRM	Voxel-wise ²	Restraint (mask) PET-PET realignment PET-MRI registration ⁷	Steeves et al., 2009

Task/ Stimulus	Tracer	Subjects	Infusion	Scans	BP derivation	Analysis	Head movement reduction/ correction	Reference
Working memory	[11C]FLB 457	12 (HV)	B	3	SRTM	ROI (MRI)	PET-PET registration ⁸	Aalto et al., 2005
Executive function	[11C]FLB 457	8 (HV)	B	2	SRTM	Voxel-wise ²	Restraint (mask) PET-MRI registration ⁷	Ko et al., 2009
Spatial attention task	[18F]Fallypride	8 (HV)	B	1	LSSRM	ROI (MRI) Voxel-wise ³	Head holder/strap PET-PET registration ⁸	Christian et al, 2006
After walking	[11C]CFT (DAT)	6 (HV) 7 (PD)	B	2(2)	Ratio	ROI (MRI) Voxel-wise ¹	Restraint (mask)	Ouchi et al., 2001

Abbreviations: dlPFC: dorsolateral prefrontal cortex; MC: motor cortex.

Subjects: HV: healthy volunteers; HV(hp) HV with high paternal care; HV(lp) HV with low paternal care; HV(PerAb) HV with perceptual aberrations; HV(PhysAn) HV with physical anhedonia; HVe: HV elderly (53-75yrs); MM: subjects with malignant melanoma; PD: subjects with Parkinson's disease; D: subjects with depression; CA: subjects with cocaine addiction; O: overweight subjects. *Infusion:* Radiotracer infusion specified as B: bolus; BI: bolus plus constant infusion. *Scans:* gives the number of scans per subject; (bs) indicates between subjects analysis; 1(2) indicates one BI scan consisting of 2 sampling periods 2(2) indicates two BI scans consisting of 2 sampling periods. *BP derivation:* gives method by which binding potential measures were derived: STRM: simplified tissue reference model (Lammertsma and Hume, 1996; Gunn et al., 1997); GA: graphical analysis (Logan et al., 1990; 1994; 1996); LSSRM linearized simplified reference region model (Alpert et al., 2003). Ratio: ratio of binding in target versus reference tissue. *Analysis:* ROI (PET/SPET/MRI): regions of interest (ROI) manually drawn on to individual PET, SPECT or MRI images.

Head movement minimisation/correction:

¹ Voxel-wise analysis performed on parametric images using the general linear approach in SPM (Friston et al., 1995).

² Voxel-wise analysis using the method of Aston et al., (2000).

³ Voxel-wise analysis method of Alpert et al., (2003).

⁴ An [11C]raclopride template in MNI space was used for spatial transformation (Meyer et al., 1999).

⁵ ROI as described by Mawlawi et al., 2001.

⁶ ROI as described by Martinez et al., 2003.

⁷ PET-to-MRI realignment on a voxel-wise basis using the method of Woods et al., (1993).

⁸ PET-PET realignment using SPM software.

⁹ PET-to-PET realignment on a voxel-wise basis using the method of Woods et al., (1992).

¹⁰ Automated re-alignment algorithm (Perruchot et al., 2004).

¹¹ Before realignment PET images were denoised using a level 2, order 5 Battle-Lemarie wavelet (Battle, 1967; Mawlawi et al., 2001; Turkheimer et al., 1999).

¹² PET-PET registration using method of Minoshima et al., (1993)

¹³ PET-PET registration according to the method of Perruchot et al., 2004.

¹⁴ Head movement monitored by Polaris system and list mode correction applied followed by FBF realignment (Kinahan and Rogers, 1989; Montgomery et al., 2006; Thielemans et al., 2006)

¹⁵ PET-to-MRI realignment using MPI-Tool, ATV.

Table 2
[11C]raclopride binding potential values obtained by re-analysis

Original gives the original values reported in Koeppe et al., (1998), where no movement correction was applied and striatal ROIs were defined using a threshold method. *ROI* gives values obtained using anatomically defined ROIs. *FBF/ROI* gives values obtained using anatomically defined ROI and movement correction using frame-by-frame (FBF) realignment. Data are reported as mean $\pm$ standard deviation. VS: ventral striatum; DS: dorsal striatum. Change in binding potential between rest and task conditions () are given as percentage change from the rest condition calculated as ((task–rest)/rest) $\times 100$.

	Right VS			Left VS			Right DS			Left DS		
	Rest	Task	(%)	Rest	Task	(%)	Rest	Task	(%)	Rest	Task	(%)
<i>Original</i>	2.27 (0.31)	1.92 (0.35)	-13.9 (20.5)	2.22 (0.28)	1.93 (0.33)	-11.8 (18.8)	2.38 (0.34)	2.22 (0.41)	-6.1 (16.1)	2.47 (0.36)	2.23 (0.42)	-8.9 (16.4)
<i>ROI</i>	2.5 (0.2)	2.4 (0.2)	-7.3 (4.1)	2.6 (0.2)	2.4 (0.2)	-4.7 (6.6)	1.9 (0.2)	1.9 (0.3)	-0.6 (14.2)	1.9 (0.3)	1.9 (0.3)	-0.3 (10.4)
<i>FBF/ROI</i>	2.1 (0.2)	2.0 (0.2)	-5.1 (10.8)	1.7 (0.2)	1.7 (0.2)	-2.8 (8.2)	2.2 (0.3)	2.1 (0.3)	-4.0 (10.4)	2.3 (0.4)	2.2 (0.3)	-5.0 (10.4)

Table 3
Results of behavioural studies of striatal dopamine release in man

Non-pharmacological studies of dopamine release are presented according to the principal process under investigation to ease comparison of results, however in several instances the stimulus and control condition may differ by more than one component. All studies were performed using [¹¹C]raclopride unless otherwise specified in the first column, only results lying within the striatum are included. The first and second columns detail the conditions under which 'stimulus' and 'control' BP measurements were made respectively; s.c.: subcutaneous injection; i.m. intramuscular injection; rTMS: repetitive transcranial magnetic stimulation; CD: compact disc. The third column presents ROI (regions of interest) from which BP measures were extracted with abbreviations as follows: R: right; L: left; ST: striatum; CA: caudate; PU: putamen; GPI: globus pallidus pars interna; d: dorsal; v: ventral; m: medial; a: anterior; p: posterior; l: lateral; r: rostral; i: intermediate; c: caudal; ab: anterior body; hd: head; PreC: pre-commissural; PostC: post-commissural; SMS: sensorimotor striatum; AST: associative striatum; LS: limbic striatum; C: contralateral; I: ipsilateral to moved limb or most affected limbs in PD. Where measures were compared in different volunteer populations, this is specified as *HV*: healthy volunteer; *PD*: Parkinson's disease; *HV*(PerAb) *HV* with perceptual aberrations; *HV*(PhysAn) *HV* with physical anhedonia; CA: subjects with cocaine addiction. Where volunteers were drug-treated this is specified as placebo, levodopa or MP (methylphenidate). The fourth column presents the percentage change in BP from ROI analysis together with the statistical significance of the finding. Percentage changes in BP marked '#' were calculated from data presented in the original publications. Negative BP values present decreases in BP in the task compared to control condition (i.e. increases in DA release). NS: non-significant; NR: not reported. The fifth column presents results from voxel-wise analyses with percentage change and statistical significance presented in brackets, with abbreviations as previously; in addition for placebo studies R: responders; NonR: non-responders. The sixth column gives any additional information or correlation of particular interest to increases in DA occurring to non-pharmacological stimuli. This includes any reported change in radiotracer delivery (R_1 or K_1).

Stimulus condition	Control condition	ROI	% BP (significance)	Voxel-wise region (significance)	Other information	Reference
<i>Motor performance and sequential motor learning</i>						
Hand Writing (I123IIBZM)	Rest	R ST L ST	~ -15 (p=0.01) ~ -9 (NS)		Age corrected	Larisch et al., 1999
Hand Writing (I123IIBZM)	Reading	R ST L ST	~ -6.0# (p<0.01) ~ -7.8# (p<0.05)		Age corrected	Schmartz et al., 2000
After 30 min. treadmill running	Rest	R PU L PU	+1.2* (NS)			Wang et al., 2000
One hour strenuous walking (I11C)CFT)	Rest	<i>HV</i> R/L CA R/L PU <i>PD</i> R/L CA R/L PU	-15.0 (p<0.05) -24.1 (p<0.05) -25.8 (p<0.05) +2.3 (NS)		No significant correlation with cadence (steps/min)	Ouchi et al., 2001
Foot extension/flexion	Rest	<i>HV</i> C dPU <i>PD</i> I dPU	-30.1# (p<0.05) -10.6# (p<0.05)		<i>HV</i> BP vs. decrease in performance (p<0.05, N)	Ouchi et al., 2002

Stimulus condition	Control condition	ROI	% BP (significance)	Voxel-wise region (significance)	Other information	Reference
Finger opposition (implicit motor memory)	Stimulus presentation			R/L CA ($t>3.0$) R/L mPU ($t>3.0$) R/L pPU ($t>3.0$)		Badgaiyan et al., 2003
Sequential finger movement	Rest	HV R CA L CA R PU L PU PD I PU	-8.3 -6.4 (R/L CA $p<0.05$) -8.8 ($p<0.05$) -5.1 ($p<0.05$) -4.2 ($p<0.05$)	HV R CA ($Z=3.53$) R PU ($Z=3.81$) L PU ($Z=4.24$)	No change R_1	Goerendt et al., 2003
Motor sequence learning	Motor control			R/L abCA ($T=3.25/2.42$) L pdmPU ($T=3.65$)		Badgaiyan et al., 2007
Motor sequence learning	Visual stimuli	R/L CA R/L PU R/L vST R/L GPi	-3.8/-6.8 (NR) -5.2/-4.3 (NR) -5.3/-6.3 (NR) -6.3/-6.1 (NR)	R/L dCA ($p<0.005$) R/L pPU ($p<0.007$) R/L aPU ($p<0.011$) L vSt ($p<0.001$) R/L GPi ($p<0.001$)	Learning speed vs. BP C GPi ($p=0.004$)	Garraux et al., 2007
Explicit motor memory task	Rest			R/L pdmPU ($T=3.80/3.38$) R/L abCA ($T=3.48/3.52$)		Badgaiyan et al 2008
Motor sequence learning Motor sequence learning Visuomotor control	Visuomotor control Rest Rest	NS R/L SMST R/L AST L SMS L AST R/L SMST R/L AST L SMS L AST	-9.3 ($p=0.05$) -11.9 ($p=0.05$) -11.1 ($p=0.03$) -12.8 ($p=0.03$) -10.0 ($p=0.03$) -9.2 ($p=0.03$) -12.4 ($p=0.03$) -9.4 ($p=0.03$)		No change R_1	Lappin et al., 2008
Thumb movement training (motor memory)	Rest	Placebo R/L dCA R/L dPU Levodopa R/L dCA R/L dPU	-3.7/-2.4 (NR) -2.0/-3.1 (NR) -10.9/-13.9 (NR) -7.2/-5.0 (NR)		dCA BP significantly greater after levodopa than placebo.	Floel et al., 2008
Reward-related stimuli						
Placebo for apomorphine (s.c. saline injection)	Rest	PD R/L hdCA R/L rPU R/L iPU R/L cPU R/L vST	-16.6 (CA $p<0.005$) -17.6 -18.2 -21.2 (Put $p<0.005$) -23.0# ($p<0.01$)		CA: BP R>NonR vStr BP R=NonR	De la Fuente-Fernandez et al., 2001, 2002
Unexpected monetary gain or loss	Rest			Gain: R vStr ($Z=2.8$) Gain: L vStr ($Z=2.92$) Loss: NS Gain vs. Loss: vStr ($Z=2.55$)	Increase in TAC (^{18}F) Gain: R/L vST ($Z=4.01/3.91$) Loss: R vSt ($Z=3.08/3.11$)	Pappata et al., 2002

Stimulus condition	Control condition	ROI	% BP (significance)	Voxel-wise region (significance)	Other information	Reference
Food stimulation (smell and taste)	Describing family genealogy	<i>Placebo</i> R/L dST R/L vST <i>MP</i> R/L dST R/L vST	-4.2# (NS) -7.5# (NS) -5.2# (NS) +0.8# (NS)		dST (control) placebo vs MP (p<0.05); control placebo vs. MP task (p<0.005). BP vs. hunger, desire for food p<0.05.	Volkow et al., 2002
Food after fasting	Fasting	R/L cCA R/L cPU R/L vST R/L dCA R/L dPU	-1.5 (NS) -2.8 (NS) +0.8 (NS) -6.8 (p=0.02) -12.4 (p=0.03)	L dPU (t=4.8) R dPU (t=6.4) R dCA (t=4.2)	Meal pleasantness vs. BP R dCA: p=0.005; vs BP R/L dPU: p=0.002.	Small et al., 2003
Placebo for caffeine	Rest	R/L CA R/L PU R/L vST	-1.1 (NS) -2.5 (NS) -5.9 (NS)		Tiredness vs. BP PU: p=0.004 No change R ₁	Kaasinen et al., 2004
Variable ratio (VR) and Fixed ratio (FR) reward schedule	Sensorimotor control (picked cards, no reward)			<i>VR-control</i> L mCA (-6.3; T=5.1) L lPU (+9.1; T=-4.4) <i>FR-VR</i> R cCA (-8.3; T=4.9) L lPU (-8.7; T=4.7) L lCA/mPU (-8.2; T=4.3)		Zald et al., 2004
Placebo rTMS	Rest	<i>PD</i> <i>More affected hemisphere</i> CA PU vST <i>Less affected hemisphere</i> CA PU vST	-11.8 (p<0.001) -13.4 (p<0.001) -11.1 (p<0.001) -8.0 (p=0.003) -9.0 (p=0.02) -7.9 (p=0.03)	Voxel-wise analysis similar to ROI results. BP was greater in more affected PU (p=0.03).	BP R vs. NonR (NS)	Strafella et al., 2006
Cocaine-associated cue video	Neutral cues (nature video)	CA R/L CA R/L PU R/L vST	-6.9# (p<0.05) -7.6# (p<0.05) -3.9# (NS)	Voxel-wise analysis showed significant (p<0.05) bilateral clusters in the striatum	BP R/L CA and R/L PU vs. craving (p<0.05). No change in K1	Volkow et al., 2006
Placebo for amphetamine	Rest	R/L vStr R/L PreC-dCA R/L PostC-dCA R/L PreC-dPU R/L PostC-dPU	-23.3 (p<0.02) -0.6 (NS) -5.1 (NS) -7.8 (NS) -8.3 (NS)	Voxel-wise analysis showed significant (p<0.05) bilateral clusters in the striatum	Drug liking, feeling excited vs. BP p<0.05	Boileau et al., 2007
Placebo during expectation of painful stimulus	No placebo during expectation of painful stimulus	L vST R vST	-11.0 (p<0.02) -8.1 (p=0.05)		R/L vST BP vs. anticipated analgesia and ratio of anticipated : perceived analgesia (p<0.005). R vST BP greater in high analgesia group.	Scott et al., 2007

Stimulus condition	Control condition	ROI	% BP (significance)	Voxel-wise region (significance)	Other information	Reference
Unpredictable reward Novel stimuli (passive task, no motor)	Rest	R/L aCA R/L aPU R/L pCA R/L pPU vStr	NS NS NS NS NS	<i>Reward</i> R/L CA (T=3.76/3.68) L lat PU (T=4.96) <i>Novelty</i> PU (T=4.5)	<i>Reward</i> Wanting vs. BP R CA and R PU (p=0.01)	Hakymez et al., 2008
Placebo effect during painful stimulus	No placebo during painful stimulus			R CA (z=5.3; -9%) R PU (z=3.9; -9%) L PU (z=5.4; -10%) R vST (z=3.6; -10%) L vST (z=4.4; -16%)	BP R vST vs. anticipated analgesia and ratio of anticipated : perceived analgesia (p<0.05); BP R/L vST, L PU vs. analgesia (p<0.05) BP L vST vs. positive affect (p=0.02).	Scott et al., 2008
Blind placebo for glucose	Open placebo for glucose	R/L PU R/L vStr	NS NS	R/L vStr (p<0.0005, decrease, men only) R/L dStr (p<0.0005, increase, men only)	No difference between lean and overweight subjects.	Hallia et al., 2008
Delayed monetary incentive task – reward condition	Neutral (control for sensorimotor and cognitive aspects)	R/L vStr R/L CA R/L PU	NS/p<0.05 NS NS	L vStr (T=2.86; p=0.008)	L vStr BP positive correlation with L midbrain and L vStr BOLD response during same task	Schott et al., 2008
Cues predicting alcohol infusion	Cues predicting Ringer's lactate infusion			R vStr (+20%)		Yoder et al., 2009
Gambling task (monetary reward and punishment)	Visual and sensorimotor control task			vStr (8.1-13.9%; p<0.05 corrected) dStr (8.2-10.2%; p<0.05 corrected)	vStr BP greater in PD patients with pathological gambling than control PD patients.	Steeves et al., 2009
Psychological and pain stress						
Arithmetic task	Rest	R/L vST R/L PU R/L CA	-9.6# (p=0.02) -7.1# (p<0.05) -4.3# (NS)	L vPU (T=6.8) R vPU (T=6.3) L vST (T=6.3) R vST (T=5.5)	Cortisol response vs. BP RL vStr: p=0.008. BP during stress significant in low but not high maternal care group (p=0.02).	Preussner et al., 2004
Arithmetic task	Counting backwards	R/L vST R/L dST	+0.8# (NS) -1.2# (NS)	No significant voxels	No relationship between maternal care or cortisol and BP	Montgomery et al., 2006
Hypertonic saline (i.m.) Hypertonic saline (i.m.)	Rest Isotonic saline (i.m.)			R/L CA (-12/-19%; p<0.01/p<0.0001) R/L PU (-13/-16%; p<0.05/p<0.0001) R vST (-12% p<0.01) R/L dCA (-11%; p<0.0001) R/L dPU (-12/-6%; p<0.0001)	Pain and pain tolerance vs. BP R CA: p<0.05 BP R CA and R PU vs. pain p<0.01	Scott et al., 2007a

Stimulus condition	Control condition	ROI	% BP (significance)	Voxel-wise region (significance)	Other information	Reference
Hypertonic saline (i.m.)	Rest			R/L vST (NS)		Scott et al., 2007b
Arithmetic task	Control task	vST HV HV (PerAb) HV (PhysAn)	+2.7 (NS) +2.6 (NS) -9.8 (p=0.03)	L dCA (-12%; p<0.005) HV (PhysAn): R/L ST (vST, PU, CA) (T=7.8) HV-NS HV (PerAb)-NS	BP vs. maternal care (p=0.015)	Soliman et al., 2008
Cognitive tasks and states						
Video game with monetary reward	Rest	R vST L vST R dST L dST	-13.9 -11.8 -6.1 -8.9 (ANOVA p<0.01)		BP vs. performance (p 0.02) R ₁ (p<0.001)	Koepp et al., 1998
Meditation to auditory relaxation CD	Same voice CD	R CA L CA R PU L PU R/L vST	-3.5 (NS) -2.9 (NS) -3.2 (NS) -1.3 (NS) -7.9 (p=0.013)		Increase in theta activity (EEG) during meditation vs. BP (p<0.05).	Kjaer et al., 2002
Retrieval with shift	Retrieval without shift	L CA R CA R aPU		-10.2% (p=0.03) -9.1% (p=0.04) -13.8% (p=0.01)		Monchi et al., 2006
Arithmetic task with monetary reward	Passive stimuli	ST Placebo MP	-5.2# (NS) -3.9# (NS)		ST control placebo vs. MP task (7.3% p<0.0001). No change in K1	Volkow et al., 2004
Spatial working memory task	Visuomotor control task	HV R/L vST R/L dCA R/L dPU PD R/L vST R/L dCA R/L dPU	HV -9.0/-2.1 (p<0.01/NS) -7.6/-2.0 (p<0.01/NS) -4.2/-1.4 (p<0.05/NS) PD -3.2/-3.0 (NS/NS) -3.8/-4.9 (NS/NS) -1.5/-2.7 (NS/NS)	HC R dCA (z=3.42)	BP in HC vs. PD (NS).	Sawamoto et al., 2008
Spatial planning task Spatial planning task Visuomotor control task	Visuomotor control task Rest Rest	R/L SMS R/L AST R/L LS R/L SMS R/L AST R/L LS R/L SMS R/L AST R/L LS	-1.3 (NS) -4.7 (NS) -0.5 (NS) -5.9 (p=0.004) -7.1 (p=0.005) -1.9 (NS) -4.5 (p=0.02) -5.4 (p=0.04) -1.0 (NS)	NS R AST (z=3.7; p=0.001) L SMS (z=3.96; p=0.01) NS		Lappin et al., 2008
Uncertain rest	Certain rest	R/L CA R/L PU	+19.7#/+14.4# (NS) +23.1#/+22.8# (p<0.05/p<0.05)	R/L PU (p<0.005)		Yoder et al., 2008