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Differential and distributed effects of dopamine neuromodulations on resting-state network connectivity

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ABSTRACT

Dopaminergic medications, used to treat neurochemical pathology and resultant symptoms in neuropsychiatric disorders, are of mixed efficacy and regularly associated with behavioural side effects. The possibility that dopamine exerts both linear and nonlinear ('inverted U-shaped') effects on cognitive neurocircuitry may explain this outcome variability. However, it has proven to be difficult to characterise neural manifestations of psychopharmacological effects in humans. We hypothesised that diverse effects of dopamine neuromodulation could be characterised using systems-level neuroimaging approaches. Using 'resting-state' functional magnetic resonance imaging (FMRI), combined with dopaminergic challenges, we examined the dopamine-dependent functional connectivity of brain 'resting-state networks' (RSNs). We compared RSN connectivity in 3 groups of healthy volunteers given dopamine antagonist (haloperidol; N = 18) or agonistic (levodopa; N = 16) drugs, or a placebo (N = 15). As RSNs have been shown to be relevant for numerous psychological functions and dysfunctions, we investigated both linear and nonlinear effects on RSN connectivity of manipulating dopamine neurotransmission pharmacologically. A basal ganglia RSN displayed both linear and nonlinear effects of dopamine manipulation on functional connectivity, respectively, with lateral frontoparietal and medial frontal neocortical areas. Conversely, a cognitive 'default mode' network showed only linear dopaminergic effects on connectivity with lateral frontal and parietal cortices. Our findings highlight diverse functional effects of dopamine neuromodulations on systems-level neural interactions. The observation that dopamine modulates distinct large-scale network connectivity patterns differentially, in both linear and nonlinear fashions, provides support for the objective utility of RSN metrics in classifying the effects and efficacy of psychopharmacological medications.

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Introduction

Dopaminergic regulation of neural processing is critical for core functions of cognition, motivated behaviour and reward response, as established by decades of animal research (Brozoski et al., 1979; Nieoullon, 2002; Schultz, 2002; Wise, 2004). Dopamine neurotransmission is also linked with impulsivity and reward-seeking behaviours in humans (Buckholtz et al., 2010; Cole et al., 2012b; Pessiglione et al., 2006). There is, therefore, considerable appreciation of the potential for dopaminergic neuromodulatory interventions to treat cognitive symptoms across a range of neuropsychiatric disorders (Cools, 2006; Goldberg et al., 1993; Robbins, 2000; Volkow et al., 2004), or even in experimental enhancement of 'normal' cognitive abilities (Cools and D'Esposito, 2011; Robbins, 2000; Volkow et al., 2009). However, the efficacy of dopamine-targeting therapies has proven extremely variable, depending on the disease or cognitive/behavioural process in question (Cools, 2006; Crow, 1980; Davis et al., 1991; Heidbreder and Newman, 2010; Laruelle et al., 2003; Martinez et al., 2011). In particular, the use of drugs to 'correct' hypo- or hyper-dopaminergic states in associated

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neuropsychiatric disorders is thought to potentiate certain sensory-motor and cognitive side effects or comorbid presentations (Cools, 2006; Dagher and Robbins, 2009; Goldberg et al., 1993).

Importantly, recent insights into understanding how brain dopamine regulates higher-level psychological functions (e.g., cognitive control and working memory) emphasise a key role for differences in baseline molecular levels in determining performance variability, both across populations and within individual subjects. In particular, it is increasingly apparent that simple 'linear' relationships, although extant in the brain (Diaconescu et al., 2010; Oei et al., 2012; Pessiglione et al., 2006), do not describe fully the complex association between dopamine levels and cognitive abilities (Cools and D'Esposito, 2011). A common observation is that both hypo- and hyper-dopaminergic states can have deleterious effects on cognitive performance, indicative of an 'inverted U-shaped' (i.e., nonlinear) association between dopamine neuromodulation and psychological functioning (Cools and D'Esposito, 2011). This could imply the existence of an 'optimum' molecular dopamine level required to balance the interplay between competing psychological processes and thus promote function. However, somewhat paradoxically this optimum level may vary, not just across different individuals and dopamine-dependent behaviours, but also across different functionally implicated brain regions (Cools and D'Esposito, 2011). This unpredictability of dopamine's ability to improve one faculty while diminishing another has significant ramifications for the psychopharmacological management of multiple neuropsychiatric disorders, including addiction, attention deficit/hyperactivity disorder, Parkinson's disease and schizophrenia.

Inverted U-shaped associations between dopamine and cognition are typically reported during the performance of prescribed cognitive tasks that activate discrete brain regions (Cools and D'Esposito, 2011). However, early evidence indicates that the 'systems-level' corollaries of dopaminergic neuronal signalling can also be probed at the level of large-scale temporal interactions, or "functional connectivity", within several cortico-subcortical and cortico-cortical cognitive control networks; including outside of specific task scenarios, when the brain is in a psychological "resting state" (Achard and Bullmore, 2007; Cole et al., 2012a; Kelly et al., 2009). Indeed, a growing body of functional magnetic resonance imaging (FMRI) literature emphasises fundamental, predictive associations between brain activity and connectivity patterns evoked during cognitive tasks and these spontaneously emerging 'resting state networks' (RSNs) (Fox et al., 2007; Pyka et al., 2009; Sala-Llonch et al., 2012; Smith et al., 2009). Furthermore, the translational value of resting-state brain activity measurements for addressing clinically relevant questions of diagnostics and prognostics is becoming increasingly apparent (Castellanos et al., 2008; Cole et al., 2010; Filippini et al., 2009; Fox and Greicius, 2010; Greicius et al., 2004; Murphy and Mackay, 2011).

Indications for nonlinear effects of dopamine neuromodulation on functional connectivity do exist in the task-based FMRI literature (Cohen et al., 2007; Wallace et al., 2011). Findings, however, appear contradictory, precluding unequivocal conclusions regarding their functional significance. We previously identified opposing (i.e., linear) systems-level effects of promoting and blocking dopamine neurotransmission, with dopamine precursor (levodopa; L-DOPA) and selective antagonist (haloperidol) pharmacological challenges respectively increasing and decreasing RSN *cortico-subcortical* functional connectivity (Cole et al., 2012b). Together with reported linear dopaminergic effects on reward processing and activity in equivalent neurocircuitry (Diaconescu et al., 2010; Oei et al., 2012; Pessiglione et al., 2006), such roles for the dopamine neurotransmitter system in modulating spontaneous large-scale neuronal interactions appear biologically plausible. Nonetheless, prior investigations may have overlooked more widespread effects (both linear and nonlinear) of dopamine modulation on network connectivity, particularly within higher-level *neocortical* circuitry. The human brain systems influenced by dopamine neurotransmission are anatomically distributed in nature throughout the cortex and subcortex and the precise mechanisms of functional integration across the regions involved in dopamine-dependent processing are not clear (Koob and Volkow, 2010; Wise, 2004; although see Cole et al., 2012a). With these caveats and the cumulative evidence from task-based neuroimaging studies in mind (Cools and D'Esposito, 2011), we reasoned that nonlinear dopaminergic drug effects might also be detectable in resting-state neural signalling patterns. We therefore examined, in data from three groups of healthy subjects reported on previously (Cole et al., 2012b), effects of broad-spectrum (agonistic and antagonistic) dopamine manipulation on the functional connectivity patterns of distinct large-scale networks, using a new analytical approach adapted to examine both linear and nonlinear systems-level connectivity relationships *across the whole brain*. Our hypotheses focussed on the 'default mode' network (DMN) and other RSNs containing reward circuitry shown to support higher-level cognitive and motivational functions (see Methods section).

Methods

Participants and study design

We recruited 55 healthy male volunteers, naïve to the experimental drugs, who were assigned randomly to three groups (L-DOPA, haloperidol or placebo). Data are reported from 49 participants who completed the study in full (mean age = 22.4 years ± 4.1 s.d.; see Table 1). Eligibility criteria were: no current (or history of) psychiatric problems as determined by the Mini-international Neuropsychiatric Interview (Sheehan et al., 1998); no medical history indicating a risk using L-DOPA or haloperidol (e.g., cardiac illness, depressive disorders, thyroid disorders, glaucoma); no current or recent use (less than 12 weeks before participation) of psychopharmacological medication and other medications or psychotropic drugs that might interfere with the central nervous system action of L-DOPA or haloperidol (e.g., cannabis or cocaine).

In a parallel design, participants received either a fixed dose of 3 mg haloperidol (Haldol®; N = 18) 4 h prior to scanning (T_{max} = 3–6 h, half-time = 14–36 h), or 100 mg levodopa combined with 25 mg of carbidopa (Sinemet®; N = 16) 1 h prior (T_{max} = 45 min, half-time = 1–2 h), or placebo (N = 15). Drug administration was double-blind and followed a previously published, 'placebo-counterbalanced' protocol (Pessiglione et al., 2006), ensuring that resting-state FMRI data were acquired at projected peak plasma concentrations for both drugs. All tablets were over-encapsulated to ensure that participants and experimenters were blind to the dosages and could not compare or identify the drugs. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center and carried out in accordance with the standards of the Declaration of Helsinki. Each participant gave signed, informed consent in which confidentiality, anonymity, and the opportunity to withdraw without penalty were assured.

Questionnaires

To assess individual differences in impulsivity, the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) was administered

Table 1
Descriptive statistics of subject variables for each drug group and associated one-way ANOVA results.

	Haloperidol (N = 18)	Placebo (N = 15)	L-DOPA (N = 16; 15 for BIS-11)	F (p)
Age (mean ± s.d.)	22.25 ± 3.53	21.47 ± 3.05	23.38 ± 5.30	0.86 (0.43)
BIS-11 total (mean ± s.d.)	66.06 ± 6.46	63.53 ± 9.01	66.67 ± 11.58	0.51 (0.61)

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