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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.

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)

immediately after ingestion of the first pill (see Table 1; data absent for a single subject in the L-DOPA group).

Image acquisition

Imaging was carried out on a 3-Tesla Achieva scanner (Philips, Best, The Netherlands) using an 8-channel head coil. A T1-weighted structural volume was acquired for registration purposes. For the resting-state FMRI scan, 220 whole-brain volumes of T2*-weighted gradient echo planar images (EPI) sensitive to blood-oxygenation level-dependent (BOLD) contrast were obtained in the axial direction (repetition time = 2.2 s, echo time = 30 ms, flip angle = 80°, isotropic voxels of 2.75 mm, slice gap = 0.25 mm, 38 slices). Participants were instructed to remain awake with their eyes closed throughout.

Image preprocessing

Resting-state FMRI data were preprocessed with tools from the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). The first four volumes were removed from each dataset to allow for magnetic equilibration, resulting in a 216-datapoint BOLD time series at each voxel per session. Preprocessing techniques applied to these data included motion correction, brain extraction, spatial smoothing with a Gaussian kernel of 5 mm FWHM and high-pass temporal filtering at 100 s. Prior to analysis, all EPI data were affine-transformed to a standard stereotactic space (MNI152 template; Montreal Neurological Institute, Montreal QC) using FSL tools, via initial registration to the associated high-resolution structural space.

Connectivity analyses: network identification

Placebo group data were entered into probabilistic multi-session independent component analysis (ICA) with temporal concatenation (as implemented in FSL MELODIC; Beckmann and Smith, 2004; Beckmann et al., 2005). We included only placebo data in this procedure to avoid biasing the definition of spatial networks towards the larger haloperidol group. This group-ICA approach decomposed the concatenated 4-D dataset (216 volumes per scan × 15 subjects = 3240 image volumes) into spatial maps of structured component signals in the data (and associated time courses), identifying component maps, including RSNs, displaying consistent spatiotemporal coherence within scans and maximal spatial independence across subjects. The number of components for the dataset was estimated automatically using the Laplace approximation to the Bayesian evidence for the model order in a probabilistic principal component model (for details see Beckmann and Smith, 2004). We identified 43 independent components in total in the placebo group FMRI data. As described previously (for details see Cole et al., 2012b), twenty of these were recognised as neurophysiologically plausible RSNs, of which eight were selected for further analyses (see Higher level analysis section) based on their neuroanatomical configurations, following a comparison with networks reported in the literature (Beckmann et al., 2005; Cole et al., 2010, 2012a; Kelly et al., 2009; Kiviniemi et al., 2009; Robinson et al., 2009; Smith et al., 2009). The remaining 23 components were deemed artefacts of motion, non-neuronal physiology or magnetic susceptibility (see, e.g., Kiviniemi et al., 2009) and thus not included in further analyses.

Connectivity analyses: measuring subject-specific RSN functional connectivity

Prior to examining our eight RSNs of interest for drug-related connectivity effects across groups, we first delineated subject-specific examples of each of the 20 viable RSNs. For this we used a 'dual regression' method (Cole et al., 2010; Filippini et al., 2009; Zuo et al., 2010), which is applied separately to each individual FMRI dataset and operates within a multiple regression framework. All 20 non-artefactual components were included in this subject-level analysis to ensure that potential extraneous interactions, or temporally overlapping relationships, between any of the eight cognitive RSNs of interest (see Higher level analysis section) and any of the 12 'nuisance' RSNs (e.g., visual, auditory or somatomotor networks) could be factored out of the analysis; effectively treating the latter as confound regressors. Voxel-wise maps of functional connectivity strength (regression coefficients) at the subject/scan level, representing 'individualised' versions of the group-level components, were calculated as follows. The full set of 20 unthresholded, weighted RSN maps identified by group-ICA of the placebo data was entered into consecutive linear model fits (spatial regression) against preprocessed, standard-space FMRI datasets from each subject's resting-state acquisition. These regressions produced separate 20-column matrices describing the mean temporal dynamics, at the individual subject/scan level, of each equivalent group-level component (one per column). These matrices were then used in consecutive linear model fits (temporal regression) against the same associated functional datasets, with the additional inclusion of time series from white matter, cerebrospinal fluid and six motion parameters to regress out artefactual signals (defined using FSL tools; for details see Cole et al., 2012b). This produced, for each FMRI acquisition, a set of 20 individualised spatial maps, each one the subject/scan-specific instantiation of an equivalent group-level RSN. These 3-D maps contained voxel-wise regression coefficient measures of network functional connectivity, which we define here as the scan-specific synchronisation between BOLD temporal dynamics at a given voxel and the mean (or 'characteristic') scan-specific BOLD time series of the individualised (RSN) component.

Higher level analysis

Further analyses examining drug effects on RSN functional connectivity focussed on a subset of eight RSNs (Figs. 1A–H), of interest due to their reported involvement in higher-order cognitive control and motivational processes potentially relevant for behavioural inhibition, reward processing or dopamine function, and related neuropsychiatric disorders (Andrews-Hanna et al., 2010; Cole et al., 2010, 2012a; Gordon et al., 2012; Greicius et al., 2004; Kelly et al., 2009; Koob and Volkow, 2010; Robinson et al., 2009; Seeley et al., 2007; Smith et al., 2009; Vincent et al., 2008). In line with this amassed literature, these RSNs are here referred to as (i) the basal ganglia/limbic network (BGLN), the (ii) anterior, (iii) posterior and (iv) ventral sub-systems of the default mode network (DMN), the (v) right- and (vi) left-lateralised frontoparietal networks, and the (vii) inferior fronto-insular and (viii) dorsal medial–lateral frontal salience/executive RSNs. The individualised whole-brain connectivity maps resulting from dual regression were first normalised to z-statistics and concatenated across subjects, creating eight 4-D files containing maps corresponding to separate subject-specific RSNs of interest, with one subject per volume (thus 49 per RSN). These RSN-specific connectivity maps were then analysed within the framework of the general linear model, using non-parametric permutation testing (5000 permutations; as implemented in the FSL 'randomise' tool) to identify regions in which functional connectivity with a given RSN of interest differed between dopamine drug treatment groups, in terms of being more strongly or weakly positive or negative. Explicitly, we tested hypotheses that both linear and nonlinear drug effects on RSN connectivity could be found, respectively, by using linear (i.e., L-DOPA > placebo > haloperidol; and the inverse) and quadratic contrasts (i.e., placebo > L-DOPA + haloperidol; and the inverse). We note that results from such quadratic contrasts are not necessarily concordant with the 'classical' inverted U-shaped model of dopamine function (however, see *Discussion* section).

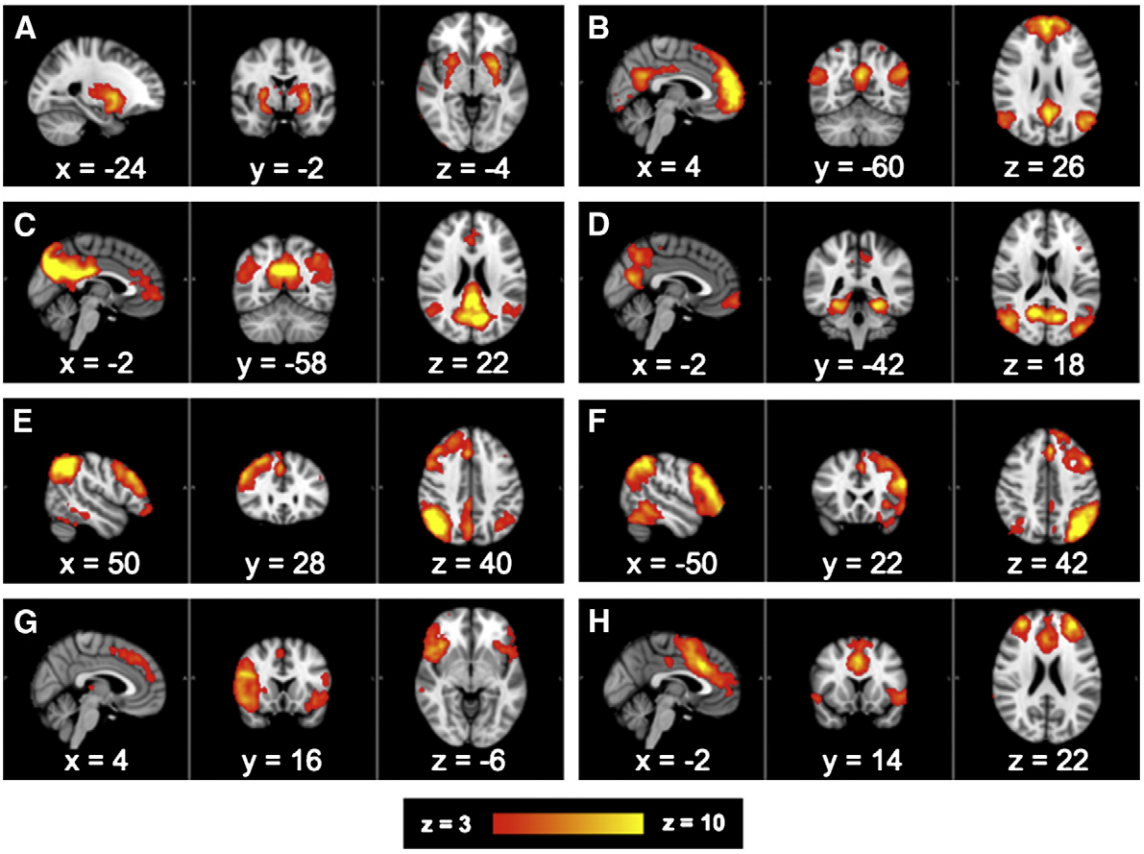

Fig. 1. Subcortical and neocortical RSNs of interest. (A–H) Eight RSNs subjected to a higher-level analysis of dopamine-dependent functional connectivity. (A) Basal ganglia/limbic RSN (BGLN) including bilateral striatum, pallidum and amygdala; (B) antero-centric default mode network (DMN); (C) postero-centric DMN; (D) hippocampal–parietal/ventral DMN; (E) right-lateralised frontoparietal network (FPN); (F) left-lateralised FPN; (G) inferior fronto-insular salience/executive network (SEN); (H) dorsal medial–lateral frontal SEN. Axial and coronal slices are presented in radiological orientation (left = right) *in all relevant figures.*

Significant effects identified by the randomise permutation testing were defined by cluster-mass thresholding using t-statistics ($t > 2.3$, $p < 0.05$) with family-wise error (FWE) correction. The whole-brain mask used for higher-level analyses was restricted to voxels where the probability of containing grey matter (on average across the entire study population, and calculated using FSL FAST) was >20%. As associations between connectivity patterns and self-report personality measures were found previously (Cole et al., 2012b), we explored within-group correlations (Pearson's r) between BIS-11 scores and the RSN connectivity scores showing regional group differences in the FMRI analysis. Based on prior associations identified by our group and others, particular focus was on any such relationships found with DMN sub-systems (Cole et al., 2012b; Gordon et al., 2012; Shannon et al., 2011). We also compared correlations across groups to investigate drug–personality interactions, by testing for significant differences between resulting opposing (Fisher z-transformed) correlation coefficients.

Results

Dopamine modulates distinct network connectivity patterns differentially

We found significant effects, both linear and nonlinear, of dopaminergic agonistic and antagonistic drug modulations on the functional connectivity patterns of two distinct, behaviourally relevant resting-state networks identified by group-ICA. A predominantly subcortical 'basal ganglia/limbic' network (BGLN; Fig. 1A), which covered the majority of the bilateral striatum and portions of the pallidum and amygdala, showed a significant linear effect of dopamine drug group (cluster $t > 2.3$, $p < 0.05$, FWE-corrected). Specifically, BGLN functional connectivity with regions of left pre- and post-central gyri/motor cortex (peak $t = 6.18$; $x = -38$, $y = -26$, $z = 42$; Fig. 2A*i*) was greater in the L-DOPA group and lower in the haloperidol group, relative to the placebo group. In addition, we found a nonlinear (quadratic) effect of dopamine drug group on the connectivity association between the BGLN and a region of dorsal anterior/mid-cingulate cortex ($t = 5.27$; $x = 4$, $y = -8$, $z = 36$), where this connectivity was significantly higher in the placebo group than in both drug groups (Fig. 2A*ii*). No significant nonlinear (inverted U-shaped or 'non-inverted' U-shaped) dopaminergic effects were identified across the whole brain in terms of functional connectivity with any *cortical* RSNs of interest.

Additionally, we found two significant linear, but opposing, effects of dopamine neuromodulation on the – predominantly neocortical – antero-centric default-mode network (DMN; Fig. 1B). These were: (i) greater connectivity in the haloperidol group, relative to placebo and then L-DOPA groups, with a cluster in the left precentral and middle frontal gyri ($t = 4.51$; $x = -40$, $y = 6$, $z = 56$; Fig. 2B*i*); and (ii) reduced (or *increased negative*) connectivity in haloperidol, relative to placebo and then L-DOPA groups, between this RSN and the right supramarginal gyrus/intraparietal sulcus ($t = 6.40$; $x = 52$, $y = -34$, $z = 46$; Fig. 2B*ii*). Furthermore, in the latter parietal cluster displaying dopamine-dependent connectivity with the DMN (Fig. 2B*ii*), this connectivity was significantly negatively correlated with subject BIS-11 scores in the group given haloperidol ($r = -0.51$, $p = 0.031$ two-tailed; Fig. 3). Non-significant equivalent correlations between DMN-supramarginal/parietal connectivity and impulsivity in the placebo and L-DOPA groups were both directionally opposite (positive) to that in the haloperidol group, to a significantly different degree ($z = 2.43$, $p = 0.015$ two-tailed) and at trend levels ($z = 1.69$, $p = 0.091$),

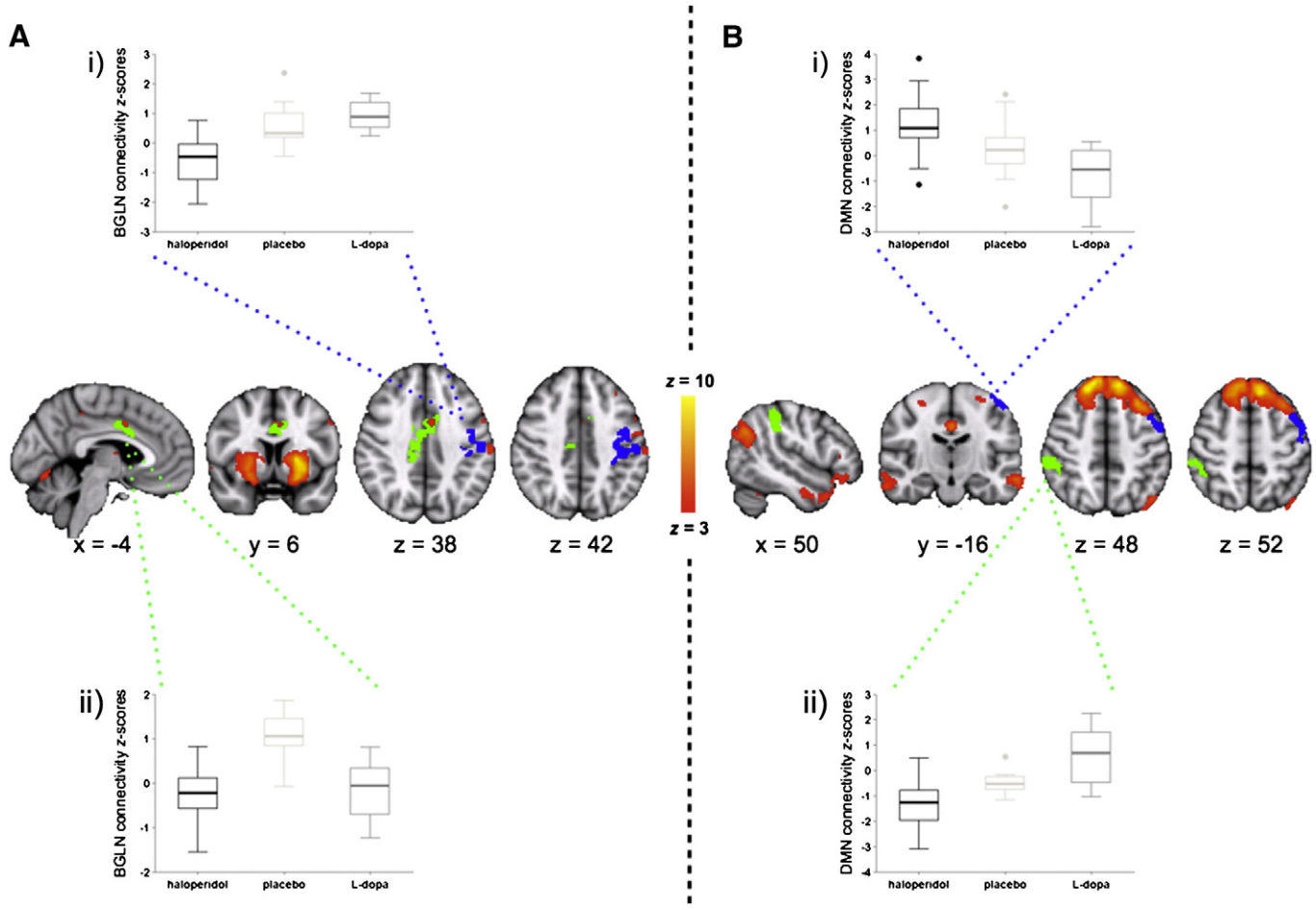

Fig. 2. Significant linear and nonlinear effects of antagonistic (haloperidol) and agonistic (L-DOPA) dopaminergic neuromodulation on large-scale brain resting-state network functional connectivity. (A) Centre; BGLN connectivity with left pre- and post-central gyri/motor cortex (blue) shows (i) a linear effect ($t > 2.3$, $p < 0.05$, FWE-corrected) of dopamine (L-DOPA > placebo > haloperidol), while BGLN connectivity with dorsal anterior-mid cingulate (green) displays (ii) a *nonlinear* effect of drug modulation (placebo > haloperidol + L-DOPA). (B) Centre; antero-centric DMN connectivity with left precentral and middle frontal gyri (blue) shows (i) an *inverse* linear drug effect (haloperidol > placebo > L-DOPA), while anterior DMN-right supramarginal gyrus connectivity displays (ii) the opposite relationship with dopamine modulation. Red-yellow overlays depict regions of high functional connectivity within the RSNs themselves, as defined by group independent component analysis.

respectively. No other connectivity patterns identified as dopamine-dependent showed similar within-group correlations or between-group interactions with BIS-11 scores.

Discussion

Dopaminergic psychopharmacological medications, used to treat neurochemical pathology and associated symptoms in multiple neuropsychiatric disorders, are often of mixed efficacy and regularly associated with adverse cognitive and sensory-motor side effects (Cools, 2006; Dagher and Robbins, 2009; Davis et al., 1991; Goldberg et al., 1993; Martinez et al., 2011). It has been posited that the apparent lack of ability to predict 'what will work for whom' with dopamine-targeting drugs is due to a pervasive nonlinearity of action, which varies across different brain systems in terms of prominence and consequence (Cools and D'Esposito, 2011). Despite intensifying neuropsychiatric interest in the potential diagnostic and prognostic value of brain 'resting-state' network activity (Cole et al., 2010; Filippini et al., 2009; Fox and Greicius, 2010; Greicius et al., 2004; Matthews et al., 2011; Murphy and Mackay, 2011), functional neuroimaging measures sensitive to these distributed systems-level connectivity phenomena have, thus far, revealed little evidence that 'inverted U-shaped' effects of dopaminergic processing, similar to

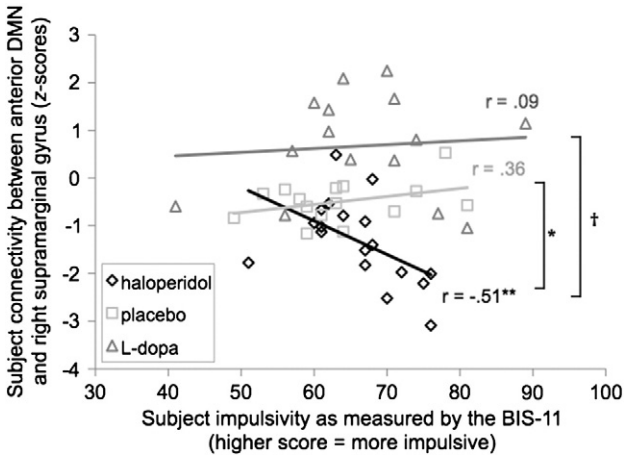

Fig. 3. Drug-specific association between DMN-parietal connectivity and impulsivity. Antero-centric DMN connectivity in right supramarginal gyrus is significantly negatively correlated with subject BIS-11 scores in the group given haloperidol ($r = -0.51$, $p < 0.05$ two-tailed, denoted by '**'), but not in the placebo or L-DOPA group. The connectivity–impulsivity correlation in the haloperidol group is significantly different to that in the placebo group ($p < 0.02$, denoted by '*') and shows trend levels of difference to that in the L-DOPA group ($p = 0.09$, denoted by '†').

those observable during prescribed cognitive tasks, are measurable in spontaneous neural signalling patterns. Nonetheless, if such effects exist, RSN functional connectivity measures should, in theory, be able to extricate them, due to the afforded ability to map biologically plausible effects on systems-level signalling throughout the entire brain (Beckmann et al., 2005; Cole et al., 2012b; Smith et al., 2009).

We here provide evidence that, relative to a placebo, dopamine agonistic and antagonistic manipulations affect large-scale resting-state network connectivity relationships in the healthy human brain in both opposing (linear) and inverted U-shaped (nonlinear) fashions. Firstly, we have demonstrated a linear, dopamine-dependent functional connectivity relationship between the basal ganglia RSN (BGLN) and regions of left somato-motor and pre-motor cortex. This is, in part, a resting-state corroboration of task-related FMRI functional connectivity results reported by Tost and colleagues, which revealed reduced connectivity between comparable left striatal and cortical regions in healthy subjects under haloperidol (dopamine antagonism) during a motor activation paradigm (Tost et al., 2010). Moreover, the current results provide intuitive confirmation that an opposing (agonistic) pharmacological manipulation with L-DOPA has the opposite effect on this same motor cortico-subcortical circuitry. Of note, the latter observation is also in line with prior electrophysiological evidence of L-DOPA increasing cortico-subcortical neuronal coupling in Parkinson's disease (Williams et al., 2002), indicating that in certain cases multimodal functional connectivity measures can provide converging evidence of neurotransmitter effects on macroscopic brain signalling.

Secondly, we have shown a nonlinear association between dopamine neuromodulation and resting-state connectivity between the BGLN and regions of dorsal anterior/mid-cingulate cortex. In contrast to the *linear* effects of dopamine drug group on cortical-BGLN connectivity subserving motor functioning (Tost et al., 2010), this observed connectivity nonlinearity might reflect the involvement of a higher-order cingulate reward circuitry implicated in the dopamine-dependent regulation, or *optimisation*, of higher-level cognitive, emotional or motivational processes (Botvinick, 2007; Bush et al., 2000; Cools and D'Esposito, 2011). The variability of action that dopaminergic drugs seem able to exert, even on two distinct, distributed interaction patterns of a single subcortical RSN, may go some way towards explaining the variability in symptom severity, treatment response, and motor and cognitive side effects observed consistently in the neuropsychiatric clinic (Dagher and Robbins, 2009; Goldberg et al., 1993; Martinez et al., 2011).

In addition to revealing differential effects of dopamine on the functional connectivity between subcortical circuitry and distinct cortical regions, we identified two separate, and opposing, linear dopaminergic effects on signalling between a predominantly anterior neocortical 'default mode' network and separate regions of the cortex. The first of these demonstrated an 'inverse linear' association (i.e., haloperidol > placebo > L-DOPA) between the pharmacological modulation of dopamine neurotransmission and DMN functional connectivity with regions of the left pre-motor cortex, while the second showed a linear group effect of dopamine neuromodulation on DMN connectivity with the right supramarginal gyrus/intraparietal sulcus regions of the inferior parietal cortex. Contrary to the majority of findings (Achard and Bullmore, 2007; Cole et al., 2012b; Tost et al., 2010; although see Diaconescu et al., 2010), the former (inverse linear) result is indicative of dopamine antagonism actually *increasing*, rather than *decreasing*, functional connectivity. While it has been hypothesised that haloperidol given acutely, via a suppressive effect on synaptic plasticity, is more likely to decrease than increase neuronal connectivity (Tost et al., 2010), this finding suggests conversely that the mechanisms by which dopamine mediates network functional connectivity *as measured by BOLD FMRI* may not be explained with such parsimony (potential differences in the neurobiological extent of action of the two medications are discussed briefly below; see also Cole et al., 2012b). With regard to interpreting the latter *linear* finding, the DMN has been widely described as "anti-correlated", or temporally negatively coupled, with frontoparietal cognitive networks involving supramarginal and intraparietal regions, and greater negative coupling between these RSNs is thought to reflect more efficient cognitive processing (Baliki et al., 2008; Cole et al., 2010; Fox et al., 2005; Hamilton et al., 2011; Kelly et al., 2008; Sala-Llonch et al., 2012; although see also Gordon et al., 2012). In comparison, the linear effect of dopamine in our data shows that haloperidol *increased negative functional connectivity* between the DMN and anterior inferior parietal regions.

The DMN is often labelled as a 'task negative' RSN, of which the angular gyrus portion of the inferior parietal cortex is an integral part (Raichle et al., 2001). Conversely, the frontoparietal RSNs, of which more anterior supramarginal and intraparietal regions form a key node, are deemed to be 'task positive' (Dosenbach et al., 2007; Fox et al., 2005; Vincent et al., 2008). This anatomical contiguity has led to the inferior parietal cortex being put forward as a "transition zone" between default mode and frontoparietal RSNs (Cohen et al., 2008; Mennes et al., 2010). In line with the common observation that these spatially distinct networks are temporally negatively coupled, it could therefore be inferred that parietal transition regions are ideally spatially situated for, or play an important part in, promoting the dynamic interplay between functionally dissociable cognitive networks. Although their primary reported finding centred on the role of anterior insula in 'driving' the switching between major cognitive RSNs, such a possibility has been suggested previously by Sridharan and colleagues (see Sridharan et al., 2008, in Supplementary discussion), based on directional, 'effective' connectivity analyses of resting-state FMRI data. It should be noted, however, that this latter study incorporated Granger causality analyses, which face important methodological caveats regarding their applicability to FMRI data (Smith et al., 2011). Nevertheless, one of the major hypothesised mechanisms by which brain dopamine acts is in mediating the dynamic balance between processes of "flexible updating and cognitive stabilization" (Cools and D'Esposito, 2011). Thus, the current finding of dopamine-dependent parietal transition region connectivity with the DMN could feasibly reflect this suggested role of the neurotransmitter in network switching relevant for efficient cognitive functioning. Although further studies are required to confirm this interpretation, initial support for the relevance of our findings for neurochemical processes underlying cognitive efficiency, flexibility or optimisation may be found in the nature of the specific DMN sub-system affected by dopamine. Of note, the sub-systems of the DMN identified in this study closely match distinct spatial patterns described previously using other functional connectivity-sensitive methods. It is, therefore, of interest to discuss the current finding in the context of purported distinct and complementary functional roles that have been ascribed to these sub-systems. We found significant linear effects of dopamine drug group on connectivity patterns of the antero-centric DMN specifically. This RSN corresponds to a sub-system implicated elsewhere in the ability to flexibly engage contextual memory mechanisms to process information efficiently and direct thought optimally, particularly that with self-referential aspects (Andrews-Hanna et al., 2010; Buckner et al., 2008). This functionality mirrors some of the proposed functional roles of (primarily prefrontal) cortical dopamine referred to above (Cools and D'Esposito, 2011). Additional support for both the behavioural functional relevance and the neurobiological plausibility of this finding stems from the drug-dependent association found here between this specific connectivity pattern and self-reported impulsivity measures, which were correlated preferentially and differentially in the group given haloperidol.

Trait impulsivity is implicated as a key factor in the functional pathology of multiple neuropsychiatric disorders associated with aberrant cognitive control, reward and dopaminergic processing (Buckholtz et al., 2010; Cools et al., 2007; Dagher and Robbins, 2009; Dalley et al., 2007; Koob and Volkow, 2010), and differences

in impulsivity have also been associated with variability in large-scale network connectivity across individuals (Cole et al., 2012b; Davis et al., 2012; Gordon et al., 2012; Shannon et al., 2011). The current finding, in particular, is in line with recent evidence showing reduced (or increased negative) functional connectivity between comparable anterior DMN and inferior parietal regions during a resting state relative to cognitive task performance, specifically in high impulsive subjects with a certain polymorphism of the dopamine transporter gene (Gordon et al., 2012). Moreover, we here expand on this previous finding by highlighting the sensitivity of this connectivity relationship to pharmacologically induced dopamine (D2) receptor blockade with haloperidol. However, it is important to note that correlations with impulsivity measures were exploratory, therefore significant results limited to only the group given haloperidol should be interpreted cautiously, as should the fact that such an association is only apparent with network connectivity relationships displaying linear, and not nonlinear, effects of dopamine modulation. Having said this, it is interesting to note that this result appears to complement strongly our previous findings of a drug-specific negative correlation, under haloperidol (but not L-DOPA or placebo), between trait impulsivity and posterior DMN connectivity with midbrain regions (Cole et al., 2012b). There is, therefore, an apparent consistency in the signature of 'drug-personality interactions' expressed within DMN connectivity patterns. The observation that these behaviour–connectivity correlations generalise to distinct, dopamine-dependent functional connectivity relationships of DMN sub-systems further emphasises that both the functional dissociations and complementarities between these RSNs are grounded in fundamental neurobiology.

One important methodological consideration for pharmacological FMRI studies is the relative benefit of using a within- or between-subjects design. Our study employed the latter, examining distinct drug conditions in three separate groups. For this 'bidirectional' investigation of connectivity, in terms of testing two distinct (agonistic and antagonist) drug conditions and a placebo condition, we envisaged that the practical benefits of scanning each participant only once, rather than requiring each to be scanned on three separate visits under different conditions, would minimise subject attrition. Moreover, in a within-subjects repeated-measures design, any variability in the potency of drug effects and participants' subjective psychological experiences could introduce order effect confounds, even into results obtained using randomised drug administration. However, within-subjects designs may provide increased sensitivity to certain types of drug effect. Thus, although our analyses were sensitive to multiple significant systems-level pharmacological effects, future studies should consider the relative pros and cons of possible design choices.

Finally, it should also be noted that, by virtue of the parallel study design, the nonlinear connectivity association presented here is not precisely analogous to the 'inverted U-shaped' conceptualisation of dopamine's cognitive influence put forward previously (see, e.g., Cools and D'Esposito, 2011). We have specifically tested, in three independent groups, the linear and nonlinear effects *on average* of increasing and decreasing dopamine neurotransmission with neuromodulatory drugs. The framework posited by Cools and D'Esposito, however, emphasises the contribution of individual differences in baseline molecular concentrations to dopamine's inverted U 'continuum'. To interpret nonlinear observations resulting from the current study as evidence of inverted U-shaped effects of dopamine levels on functional processing requires the assumption that, prior to drug administration, subjects in the three experimental groups did not differ, on average, in their basal brain dopamine levels. Although this assumption is well founded, it cannot be confirmed unequivocally from the current data. In favour of this assumption, however, is the recent finding that a similar, functionally relevant inverted U-shaped effect on cognitive performance is observable across distinct individuals given distinct doses of a single drug: L-DOPA (Chowdhury et al., 2012). Nonetheless, it is important to note that the neurochemical specificity of both L-DOPA and haloperidol remains debatable and that their precise mechanisms of action are not entirely opposite. Dopamine neurotransmission is increased indirectly by L-DOPA, which promotes dopamine synthesis and may have knock-on effects on other neurochemical systems (Dolphin et al., 1976; Everett and Borcherding, 1970), while haloperidol blocks dopamine D2 receptor function preferentially but not entirely selectively (e.g., Kroeze et al., 2003). These mechanistic differences may explain to some extent why the current findings identify both linear and nonlinear dopamine drug effects on large-scale network functional connectivity patterns. Therefore, future neuroimaging studies investigating the 'inverted U' hypothesis may benefit from administering repeated or varying doses of dopaminergic drugs with quantifiable mechanisms of action, or through combining resting-state FMRI and positron emission tomography neuroreceptor imaging methodologies (see Cole et al., 2012a). Studies providing within-subjects measures to elucidate how baseline dopamine levels or receptor availabilities influence the reactivity of brain functional networks to selective pharmacological challenges will, in this way, provide valuable mechanistic information complementary to the current findings. Furthermore, such multimodal imaging investigations would only benefit from the additional inclusion of genotyping procedures (see, e.g., Gordon et al., 2012; Liu et al., 2010), to cross-examine the genetic, neurobiological and neurochemical factors influencing endophenotypic, large-scale network functional connectivity measures of individual differences in the response to experimental interventions such as dopamine manipulation.

We conclude that, despite the incomplete standardisation of resting-state network connectivity measures for assessing clinical diagnosis, prognosis and treatment efficacy, their ability to characterise biologically plausible linear and nonlinear effects of broad-spectrum pharmacological (dopamine) modulations, at the systems level, supports their continued application and development as useful markers for these purposes in neuropsychiatry and medicines development.

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Conflict of interest

The authors have no conflicts of interest to declare.

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