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Age-differential relationships among dopamine D1 binding potential, fusiform BOLD signal, and face-recognition performance

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A B S T R A C T

Facial recognition ability declines in adult aging, but the neural basis for this decline remains unknown. Cortical areas involved in face recognition exhibit lower dopamine (DA) receptor availability and lower blood-oxygen-level-dependent (BOLD) signal during task performance with advancing adult age. We hypothesized that changes in the relationship between these two neural systems are related to age differences in face-recognition ability. To test this hypothesis, we leveraged positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to measure D1 receptor binding potential (BP_{ND}) and BOLD signal during face-recognition performance. Twenty younger and 20 older participants performed a face-recognition task during fMRI scanning. Face recognition accuracy was lower in older than in younger adults, as were D1 BP_{ND} and BOLD signal across the brain. Using linear regression, significant relationships between DA and BOLD were found in both age-groups in face-processing regions. Interestingly, although the relationship was positive in younger adults, it was negative in older adults (i.e., as D1 BP_{ND} decreased, BOLD signal increased). Ratios of BOLD:D1 BP_{ND} were calculated and relationships to face-recognition performance were tested. Multiple linear regression revealed a significant Group × BOLD:D1 BP_{ND} Ratio interaction. These results suggest that, in the healthy system, synchrony between neurotransmitter (DA) and hemodynamic (BOLD) systems optimizes the level of BOLD activation evoked for a given DA input (i.e., the gain parameter of the DA input-neural activation function), facilitating task performance. In the aged system, however, desynchronization between these brain systems would reduce the gain parameter of this function, adversely impacting task performance and contributing to reduced face recognition in older adults.

1. Introduction

Performance in many cognitive domains declines with advancing adult age (e.g., Bäckman et al., 2001, 2006; Di et al., 2014; Nyberg et al., 2009, 2012; Persson et al., 2005; Rönnlund et al., 2005; Rypma and Prabhakaran, 2009; Salthouse, 1994, 1996; Schaie, Willis, & O'Hanlon, 1994). One cognitive domain that deteriorates in aging is face recognition (Bartlett and Fulton, 1991; Grady et al., 1994, 2000; Grady and Craik, 2000; Gunning-Dixon et al., 2003; Lamont et al., 2005). For instance, older adults have an increased tendency to erroneously judge novel faces as ones they know or have seen before compared to younger adults (e.g., Bartlett and Fulton, 1991; Edmonds et al., 2012; Memon et al., 2003).

Much work in cognitive neuroscience converges on the notion that face processing depends upon a network of brain areas, featuring a "core system" and an "extended system," during encoding and recognition (Gobbini and Haxby, 2007; Haxby et al., 2000; Ishai, 2008). These systems comprise multiple cortical regions, including visual areas (e.g., inferior occipital cortex), episodic-memory areas (e.g., insula, temporal cortex), affective structures (e.g., amygdala, anterior cingulate cortex), as well as a region that is especially active during face processing, fusiform gyrus (FFG). Many of these face-processing regions are structurally altered in aging. Specifically, occipital cortex (Salat et al., 2004) and medial temporal-lobe structures, such as FFG (Raz et al., 2005; Kennedy and Raz, 2009), show age-related cortical thinning.

Neural activity during face processing is also altered in advanced age (e.g., Grady et al., 1994, 2000; Zebrowitz et al., 2016). Grady et al. (1994) contrasted performance on face-matching and location-matching tasks and observed slower performance by older adults during face matching along with reduced blood flow in visual cortex. Another study found that older adults were slower and less accurate than younger adults while matching degraded and non-degraded faces (Grady et al., 2000). These authors also observed age-related differences in blood-oxygen-level dependent (BOLD) signal in multiple cortical regions.

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Subsequent work focusing on specific nodes of the face-processing network has reported age-related changes in those regions involved in emotion processing (e.g., Fischer et al., 2005, 2010; Gunning-Dixon et al., 2003; Szymkowicz et al., 2016; Tessitore et al., 2002; Wright et al., 2008; Ziaei and Fischer, 2016), gaze estimation (e.g., Ziaei and Fischer, 2016), and face detection in complex contexts (e.g., Graewe et al., 2012). Taken together, these studies suggest that age-related deficits in face processing reflect underlying structural and functional changes in cortical regions comprising the face-processing network. What remains to be understood is the role that neurochemical factors could play in such age differences.

Dopamine (DA) is implicated in performance of many cognitive tasks (Bäckman et al., 2006, 2011a; 2011b; Guitart-Masip et al., 2015; Papenberg et al., 2014; Roffman et al., 2016; Salami et al., 2019), plays a critical role in the modulation of cognitive control (Cools, 2008, 2015; Cools & D'Esposito, 2011; van Schouwenburg et al., 2010, 2012; 2013; Westbrook and Braver, 2016), and could affect both task-based (Klostermann et al., 2012; Nagano-Saito et al., 2008) and resting-state (Gordon et al., 2013; Nagano-Saito et al., 2017) functional connectivity. Binding potential (BP_{ND}) for both D1 (e.g., Dagher et al., 2001; Karlsson et al., 2009; Ouchi et al., 1999; Rieckmann et al., 2011; Rypma et al., 2015; Suhara et al., 1991) and D2 (e.g., Glickstein et al., 2002, 2004; Li et al., 2013; Luciana and Collins, 1997; MacDonald et al., 2009; Volkow et al., 1998a) receptors has been linked to cognitive performance and shows pronounced decreases across the adult life span (Antonini et al., 1993; Kaasinen et al., 2000; Kaasinen and Rinne, 2002; Rinne et al., 1990; Suhara et al., 1991; Volkow et al., 1998b; Wang et al., 1998). In fact, increasing adult age is more negatively associated with D1 receptors than with either D2 receptors or DA synthesis capacity (Karrer et al., 2017).

Research has demonstrated the importance of DA for episodic memory (Bäckman et al., 2000; Cervenka et al., 2008; Nyberg et al., 2016; Takahashi et al., 2007) as well as a relationship of DA to BOLD signal (Cabeza et al., 2017; Lohrenz et al., 2016; Mandeville et al., 2013; Rieckmann et al., 2011; Rypma et al., 2015; Schott et al., 2008; Zaldivar et al., 2014). Animal models have elucidated a plausible mechanism by which DA release in striatum triggers activation of DA receptors, leading to increased BOLD signal (see Knutson and Gibbs, 2007), and have proven capable of describing various and conflicting results from prior literature (Mandeville et al., 2013). One study (Mandeville et al., 2013) tested a model of dopaminergic modulation of cortical and subcortical BOLD signal from PET (using raclopride) and functional magnetic resonance imaging (fMRI) in non-human primates. Results from testing the multireceptor model they developed demonstrated that BOLD signal resulted from a confluence of excitatory D1 receptor activity and inhibitory D2 receptor activity. Pharmacologic manipulation studies in humans have provided some of the best evidence for relationships between task-evoked cortical BOLD signal and the DA system (Breiter et al., 1997; Kim et al., 2010; Kufahl et al., 2005; Mattay et al., 2000; Völlm et al., 2004). Kim et al. (2010), for instance, measured BOLD signal during language processing, wherein either L-DOPA or placebo was administered to participants. They observed greater BOLD signal following L-DOPA administration compared to placebo within several regions of the face-processing network, including fusiform, occipital, and cingulate cortex (see also Tivarus et al., 2008). These results implicate DA as a modulator of BOLD signal in face-processing regions. The formation of episodic memories via long-term potentiation has also been posited to depend upon a DA-modulated circuit in which hippocampal projections to the ventral tegmental area (VTA) facilitate DA release in FFG (Lisman et al., 2011; Schultz, 2007).

Beyond episodic memory in general, DA is thought to play a role in components of the face-processing network (Skuse and Gallagher, 2009). Evidence suggests that DA modulates amygdalar BOLD signal in response to variations in facial attractiveness (Aharon et al., 2001; Kampe et al., 2001; Liang et al., 2010; Senior, 2003). DA might also influence BOLD signal in face recognition, as seen in one study that observed a strong association between D1 BP_{ND} and BOLD signal in FFG in younger adults (Rypma et al., 2015). Moreover, the relationship between DA and BOLD signal (i.e., the BOLD:D1 BP_{ND} ratio) was linked to face-recognition performance in the same region. The BOLD:D1 BP_{ND} ratio indexes the amount of task-relevant BOLD signal elicited by a given unit of D1 BP_{ND}; individuals with a greater BOLD response for a given level of receptor availability would have a greater BOLD:D1 BP_{ND} ratio. Genetic studies also provide evidence for the role of dopamine in face processing, with some showing consequences of genetic variability (in, e.g., COMT val158met, DARPP-32) for face recognition performance (Lamb et al., 2016; Papenberg et al., 2017) and even BOLD signal in response to faces (Persson et al., 2017). Such variable modulation of BOLD signal has been posited to underlie age-related changes in cognitive performance at the network level (Rieck et al., 2017). Thus, age-related alterations in face-recognition performance might be a consequence of changes to the DA-BOLD relationship.

We used positron emission tomography (PET) and the SCH23390 radioligand to examine the relationship of DA D1 BP_{ND} to BOLD signal in cortical regions that comprise the face-recognition network. BOLD signal was measured during performance of a face-recognition task using fMRI. Because DA D1 receptor availability decreases with age (Rieckmann et al., 2011; Rinne et al., 1990; Suhara et al., 1991; Wang et al., 1998) and appears to be involved in modulation of BOLD signal in FFG (Rypma et al., 2015), we expected differences in DA-BOLD modulation between older and younger participants. Because it is known that face-recognition performance deteriorates in aging (e.g., Bartlett and Fulton, 1991; Edmonds et al., 2012; Memon et al., 2003), we also examined age-differential relationships between DA-BOLD dynamics and face-recognition performance.

2. Materials and methods

2.1. Participants

Twenty younger participants (M = 25.2 years, SD = 2.2; 10 females) and 20 older participants (M = 70.4 years, SD = 3.1; 10 females) were recruited via ads placed in a local newspaper and around the Stockholm metropolitan area. The younger sample was included in the Rypma et al. (2015) study. Data collection for both younger and older participants occurred contemporaneously over a fifteen-month span under a single experimental protocol. Participants reported that they were nonsmokers with no history of drug or alcohol abuse, significant neuropsychiatric disorders, or neurological insults, and all provided written informed consent. Experimental procedures were approved by the Karolinska Institute Institutional Review Board, and [^{11}C] SCH23390 dosage levels used during PET imaging were approved by the Ethics and Radiation Safety Committees of the Karolinska Institute, Stockholm, Sweden. Participants whose behavioral accuracy was either (1) > 2.5 SDs below their group mean, or (2) lower than their false-alarm rates, were excluded from analyses: outlier 1 (older male) accuracy = 9%; outlier 2 (older male) accuracy = 27%; outlier 3 (younger male) accuracy = 14%; outlier 4 (younger male) accuracy = 18%. The final number of participants included for subsequent analyses were 18 younger participants (M = 25.3 years, SD = 2.3; 10 females) and 18 older participants (M = 70.2 years, SD = 3.2; 10 females).

2.2. Procedure

Following collection of informed consent, participants completed health and cognitive screening measures. Afterwards, a PET scan (61 min duration) was conducted to acquire D1 BP_{ND} data. Following PET scanning (never more than 1 week later), participants returned for MRI scanning to acquire BOLD data. At this time, participants also completed several cognitive measures, including a verbal fluency task (with both letter and category as stimuli), subject-performed task, computation span, Wisconsin Card Sort task, word comparison task, figure comparison task, and letter comparison task.

2.3. Stimuli

Color photographs depicting 12 younger women, 12 younger men, 12 older women, and 12 older men with neutral facial expressions were selected from the FACES database (Ebner et al., 2010). Six faces of each age-gender combination were selected for encoding, resulting in 24 targets, and the remaining 24 faces served as lures during the recognition phase. Target and lure faces were counterbalanced across participants.

2.4. Behavioral task

Prior to entering the fMRI scanner, participants were presented with 24 faces and asked to encode them with the following instructions: "You will now see a number of faces. Your task is to remember them for a later test." During fMRI scanning, on each trial of the face-recognition task, participants were presented with either a target (shown during encoding) or a lure (novel) face, presented for 2 s each. Between each trial, a crosshair appeared on the screen for 500 ms. Examples of face stimuli, and a depiction of the task structure, can be seen in Fig. 1. Participants responded via button-press to indicate whether or not they recognized the face from the 24-face set they encountered outside the scanner. Blocks of face-recognition trials were alternated with blocks of simple sensorimotor trials, also presented for 2 s with a 500 ms inter-trial interval, during which participants responded via button-press when either a cross or a circle appeared at center screen. The task was presented in two runs, each comprising 2 sets of 4 blocks (for a total of 8 face-recognition and 8 sensorimotor blocks). Each block lasted 15 s, with an inter-block interval of 1.25 s, resulting in a total length of 130 s per run. During each face-recognition block, participants viewed three novel faces and three target faces. These tasks were performed in the context of a larger battery that included spatial working memory and cognitive interference tasks (Bäckman et al., 2011a; Fischer et al., 2010; Rieckmann et al., 2011).

2.5. fMRI scanning and analysis

Whole-brain imaging data were acquired on a 1.5 T Signa Echospeed MR-scanner (GE Medical Systems, Waukesha, Wisconsin), using a standard circular 1-channel head coil. T1-weighted 3DSPGR images (TR = 24 ms, TE = 6 ms, flip angle = 35°) were acquired for anatomical co-registration in 124 contiguous 1.5 mm coronal slices (image resolution = 256 × 256 × 186 mm, voxel size = 0.9 × 0.9 × 1.5 mm). Functional images were acquired using a T2*-sensitive gradient-echo EPI sequence (TR = 2.5 s, TE = 40 ms, flip angle = 90°). The image volumes had a field of view of 220 mm × 220 mm, an in-plane resolution of 3.44 mm × 3.44 mm, and contained 32 horizontal, 4-mm-thick slices with a 0.5 mm gap in between slices. During the fMRI session, 104 volumes were obtained across the two scanning runs.

Functional images were spatially realigned to the first volume in each time series. Inspection of movement parameters generated during the spatial realignment showed that no participant had moved in excess of 3 mm or 3° in any direction during task performance. The six movement parameters were also included as covariates in the first-level analysis. Volumes were then normalized to the standard MNI/ICBM152 T1 template from SPM. Normalized images were spatially smoothed using a Gaussian kernel with a full-width-at-half-max (FWHM) of 12 mm and low-pass filtered (128 Hz).

Face-recognition versus sensorimotor BOLD effects were modeled using a box-car function convolved with a canonical hemodynamic response function (that also acted as the high-pass filter; Sauvage et al., 2017). Whole-brain analyses were performed using directional *t*-tests of face-recognition versus sensorimotor periods. Average β values were then extracted from regions of interest (ROIs), which comprised 4 mm radius spheres centered around peak signal (*t*-score) within anatomical brain regions of the WFU Pick atlas (Maldjian et al., 2003), consistent with previous work (Bäckman et al., 2011a). ROIs comprising the face-processing network (Gobbini and Haxby, 2007; Haxby et al., 2000; Ishai, 2008) included anterior cingulate, amygdala, FFG, and inferior

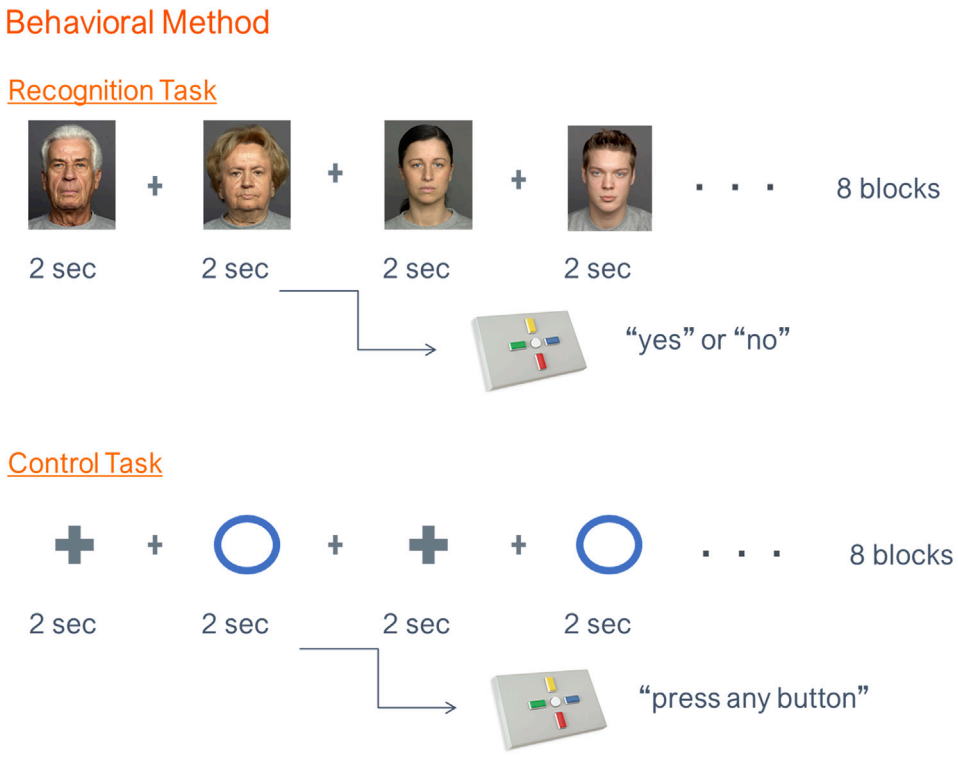

Fig. 1. Behavioral paradigm of the face-recognition task performed in the scanner. During the recognition task, participants indicated whether they recognized faces presented every 2 s as being part of a set that they saw prior to scanning. During the control task, participants responded by button-press any time they saw either a cross or a circle.

occipital gyrus.

2.6. PET scanning and DA D1 analysis

PET data were collected on an ECAT Exact HR47 system (Siemens, Erlangen, Germany) in 3D mode with transaxial resolution of 3.8 mm full-width at half-maximum and a field of view of 4.5 mm radially 20 mm from center. Transmission measurements were collected over 10 min with 3 rotating 68Ge-68Ga sources. Then, 300MBq of the [^{11}C] SCH23390 radioligand was rapid-bolus injected into the left antecubital vein. Emission data were collected over the following 51 min in 13 time frames of increasing duration. Because PET data were collected at rest (i.e., participants were not performing a task during PET scanning), and in order to parallel previous analytical techniques (Bäckman et al., 2011a; Rypma et al., 2015), the functional ROI approach used in fMRI data analysis was not employed. Instead, ROIs were manually delineated on each individual's T1-weighted image separately for each hemisphere using the Human Brain Atlas software (HBA; Roland et al., 1994). ROIs derived for subsequent analyses were part of the "core" and "extended" systems of the face-processing network (Gobbini and Haxby, 2007; Haxby et al., 2000; Ishai, 2008), and included FFG, amygdala, insula, anterior and posterior cingulate cortex, occipital cortex, and parietal cortex (Rieckmann et al., 2011). Correction for partial-volume effects followed the approach used by Meltzer et al. (1990). Briefly, HBA-derived ROIs were segmented into gray matter, white matter, and CSF. CSF was masked out of ROIs, and the resulting gray- and white-matter images were blurred with a Gaussian smoothing kernel (FWHM = 12 mm) to better match the spatial resolution of PET, allowing derivation of a correction factor for each smoothed ROI. Subsequent analyses with unilateral ROIs did not produce different results; therefore, we aggregated data from unilateral ROIs across hemispheres.

2.7. BP_{ND} calculation

Time-activity curves (TACs) were calculated from the PET images. For TAC generation, radioactivity was plotted versus time and corrected for decay rate. D1 receptor availability was measured as the BP_{ND} of the [^{11}C]SCH23390 radioligand. BP_{ND} is defined as the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue (Innis et al., 2007) and calculated using the simplified reference tissue model with cerebellum as the reference region, because of negligible expression of DA D1 receptors (Lammertsma and Hume, 1996), and corrected for partial-volume effects (Meltzer et al., 1990; see also Greve et al., 2016). Thus, BP_{ND} reflects D1 receptor availability, indexed by the extent of radioligand occupancy at postsynaptic D1 receptors.

3. Results

3.1. Cognitive task performance

Group-level performance on the cognitive battery (administered outside the scanner environment), and group-level measures of years of education and estimated salary, are reported in Table 1.

3.2. In-scanner task performance

Younger adults performed significantly faster (mean $RT_Y = 364.2$ ms [*SEM* = 13.2 ms]) on the sensorimotor control task than older adults (mean $RT_O = 492.0$ ms [*SEM* = 23.1 ms]; $t(34) = 4.79$, $p < 0.001$). Face-recognition accuracy, as measured by *d'* (Snodgrass and Corwin, 1988), was significantly lower in older compared to younger adults (mean $z_Y = 0.56$ [*SEM* = 0.25] vs. mean $z_O = -0.56$ [*SEM* = 0.20]; $t(34) = -3.48$, $p = 0.001$), reflecting higher recognition performance in the young. This pattern replicates the bulk of past research on this topic (e.g., Bartlett and Fulton, 1991; Edmonds et al., 2012; Grady and Craik, 2000; Gunning-Dixon et al., 2003; Lamont et al., 2005; Memon et al., 2003).

Table 1
Age-group differences in demographics and neuropsychometric task performance.

ROI	Younger group mean (SD)	Older group mean (SD)	*t*-score (df = 35)	*p*-value
Education, years	15.18 (2.16)	14.31 (4.20)	0.67	$p = 0.505$
Estimated salary, SEK	34,493 (6,106)	35,662 (5,409)	0.55	$p = 0.586$
Letter fluency, items generated in 30 s	17.38 (3.64)	17.53 (3.26)	0.12	$p = 0.902$
Category fluency, items generated in 30 s	21.67 (5.64)	19.38 (2.99)	1.46	$p = 0.151$
Free recall of actions, items recalled in 2 min	11.39 (2.09)	9.39 (3.05)	2.28	$p = 0.029$
Vocabulary, number correct	29.56 (2.41)	33.39 (1.91)	5.22	$p < 0.001$
Wisconsin card-sorting task, total trials correct	66.59 (4.74)	71.72 (9.77)	1.97	$p = 0.057$
Figure comparison, average score across two trials	21.25 (3.40)	15.74 (2.42)	5.42	$p < 0.001$
Letter comparison, average score across two trials	9.47 (3.01)	7.69 (2.09)	2.05	$p = 0.048$

3.3. Age-group differences in D1 BP_{ND} and BOLD signal

Across regions, D1 BP_{ND} was significantly higher in younger than in older adults. The main effect of age group was significant as indicated by MANOVA, $F = 7.67$ ($p < 0.001$), as were group differences within all regions, except amygdala (corrected $p < 0.05$; Table 2). Similarly, BOLD signal was significantly greater across regions in younger than in older adults. The main effect of age group was significant, $F = 3.18$ ($p = 0.010$). Group differences within regions were not significant when corrected for multiple comparisons (corrected $p > 0.05$; Table 3). The face-recognition task used reliably elicited BOLD signal in regions of the face-processing network, with the greatest magnitude of BOLD signal change occurring in FFG (Fig. 2).

3.4. D1 BP_{ND}-BOLD relationships across age

To test for age-related differences in DA-BOLD relationships, we performed a univariate regression analysis to assess relationships between D1 BP_{ND} and BOLD signal magnitude in each ROI. In FFG, younger adults' D1 BP_{ND} strongly predicted BOLD signal ($\beta = 0.13$, $r = 0.61$, $p = 0.007$). Older adults' D1 BP_{ND} also predicted BOLD signal in FFG, but in the opposite direction ($\beta = -0.09$, $r = -0.65$, $p = 0.003$). For older

Table 2
Age-group differences in D1 BP across ROIs.

ROI	Younger group mean (SD)	Older group mean (SD)	*t*-score (df = 34)	*p*-value
Anterior cingulate cortex (ACC)	0.495 (0.256)	0.372 (0.195)	4.01	$p < 0.001$
Amygdala	0.372 (0.203)	0.302 (0.171)	1.78	$p = 0.084$
Fusiform gyrus (FFG)	0.371 (0.195)	0.296 (0.152)	3.24	$p = 0.002$
Insular cortex	0.584 (0.304)	0.425 (0.221)	4.96	$p < 0.001$
Occipital cortex	0.444 (0.233)	0.384 (0.199)	2.22	$p = 0.032$
Parietal cortex	0.476 (0.257)	0.390 (0.202)	2.64	$p = 0.012$
Posterior cingulate cortex (PCC)	0.416 (0.219)	0.327 (0.170)	3.44	$p = 0.001$

Table 3
Age-group differences in BOLD signal across ROIs.

ROI	Younger group mean (SD)	Older group mean (SD)	*t*-score (df = 34)	*p*-value
Anterior cingulate cortex (ACC)	0.413 (0.283)	0.491 (0.295)	0.55	$p = 0.588$
Amygdala	0.068 (0.074)	0.104 (0.164)	0.23	$p = 0.820$
Fusiform gyrus (FFG)	0.673 (0.438)	0.656 (0.407)	0.62	$p = 0.541$
Insular cortex	0.070 (0.269)	0.161 (0.140)	0.21	$p = 0.833$
Occipital cortex	0.581 (0.382)	0.406 (0.253)	2.34	$p = 0.024$
Parietal cortex	0.530 (0.351)	0.512 (0.338)	0.93	$p = 0.359$
Posterior cingulate cortex (PCC)	−0.008 (0.371)	0.155 (0.251)	0.11	$p = 0.911$

adults, similar effects were observed in insula ($\beta = -0.26$, $r = -0.55$, $p = 0.019$). No significant relationships were observed in either age group in other ROIs ($p > 0.05$; Fig. 3). To formally test whether DA-BOLD relationships differed between younger and older adults, we used a common univariate regression framework to predict individuals' BOLD signal from their D1 BP_{ND}. Linear regression predicting BOLD from Group and D1 BP_{ND} revealed a significant main effect of D1 BP_{ND}, $F(1,32) = 19.20$ ($p < 0.001$). Further, a significant Group × D1 BP_{ND} interaction effect was observed, $F(1,32) = 19.07$ ($p < 0.001$; Fig. 4), indicating a significant difference in the nature of the relationship between dopaminergic (D1 BP_{ND}) and neurovascular (BOLD) systems in younger and older adults.

3.5. D1 BP_{ND}-BOLD ratio vs. performance

Based on the observation that D1 BP_{ND} in FFG predicted FFG BOLD signal, but in opposite directions for younger and older adults, we assessed the relationship between these two measures and performance. For both age groups, we noticed that among individuals with high *d'* scores (i.e., those participants whose face-recognition scores were above their group median), most data points fell along or above the DA-BOLD regression line (Fig. 2). These observations suggest that, for these participants, there was greater BOLD signal relative to D1 receptor availability compared to those with low *d'* scores, and that performance might depend upon the relationship between BOLD and D1 BP_{ND} rather than either factor alone. Indeed, neither BOLD nor D1 BP_{ND} in FFG alone was associated with face-recognition performance in either age group ($p > 0.05$ in both cases).

To formally test whether DA-BOLD relationships differentially influenced performance in younger and older adults, we calculated a ratio of BOLD:D1 BP_{ND} signal for each participant's ROI, and used linear regression to predict individuals' *d'* scores from their BOLD:D1 BP_{ND} ratio. Linear regression predicting *d'* from Group and BOLD:D1BP_{ND} ratio revealed a greater slope for younger ($\beta = 0.64$) than for older ($\beta = 0.01$) adults. Further, a significant Group × BOLD:D1BP_{ND} Ratio interaction effect was observed, $F(1,32) = 5.36$ ($p = 0.027$; Fig. 5). A Mahalanobis distance analysis was performed to identify outliers present in the analysis, and no outliers were identified.

4. Discussion

This study examined age differences in face-recognition performance, D1 BP_{ND}, and BOLD signal in brain regions associated with face processing. In agreement with extant findings (e.g., Bartlett and Fulton, 1991; Edmonds et al., 2012; Grady and Craik, 2000; Gunning-Dixon et al., 2003; Lamont et al., 2005; Memon et al., 2003), we observed lower recognition accuracy for older compared to younger adults. Across the entire face-processing network, both D1 BP_{ND} and BOLD signal were greater in younger compared to older adults. D1 BP_{ND} significantly predicted BOLD in both age groups, but in opposite directions, and only in FFG, despite the lack of a significant age-group difference in BOLD in this ROI. In this face-processing region, higher D1 BP_{ND} was associated with higher BOLD signal in the young, but with lower BOLD signal in the old. Finally, whereas neither BOLD nor D1 BP_{ND} alone were associated with face recognition, the ratio of D1 BP_{ND} to BOLD in FFG predicted face recognition for younger, but not for older, adults. These results suggest that the interrelationship between DA and BOLD, upon which face-recognition performance depends in younger adults (Rypma et al., 2015), is altered in aging (Bäckman et al., 2011a).

The link between D1 BP_{ND} and BOLD observed in younger adults' FFG is consistent with that observed in other brain regions using other tasks (Gibbs & D'Esposito, 2005; Guitart-Masip et al., 2015; Weiland et al., 2014). Studies have examined this relationship during working memory (for a review, see Bäckman and Nyberg, 2013), and found a DA-BOLD association in younger adults. Striatal DA is also related to BOLD signal in both striatum and cortical regions during performance of multiple cognitive tasks, including working memory (Bäckman et al., 2010,

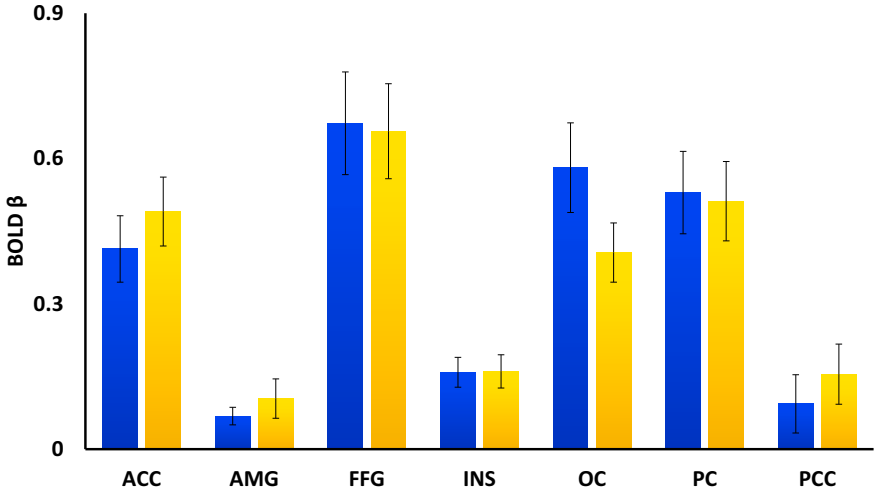

Fig. 2. BOLD β in each ROI of the face-processing network measured during performance of the face-recognition task for younger (blue) and older (yellow) groups. Task data were modeled by convolving the hemodynamic response function with a box-car function representing the face-recognition blocks during the task. The task reliably elicited BOLD signal in regions of the face-processing network, with the greatest magnitude of BOLD signal change occurring in FFG.

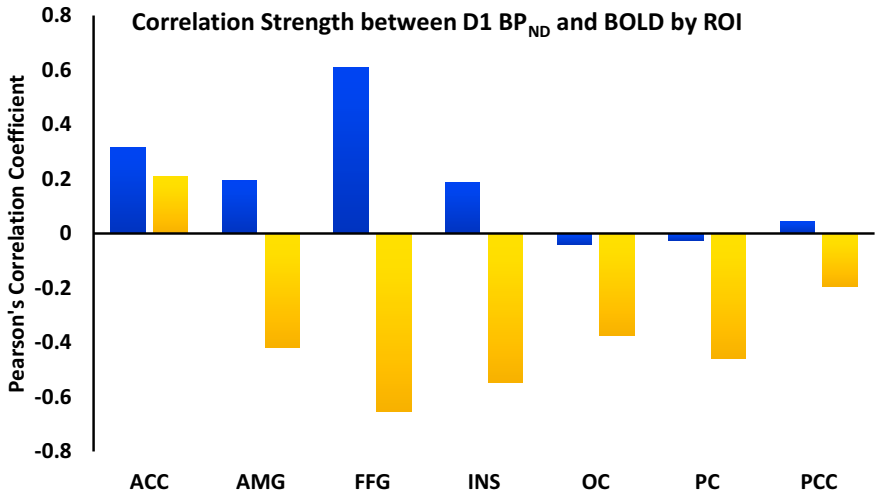

Fig. 3. Correlation coefficients of (Pearson's *r*) between D1 BP and BOLD in each ROI for younger (blue) and older (yellow) groups. Significant correlations were observed in FFG for both groups, as well as in insula for older adults ($p < 0.05$). ACC = anterior cingulate cortex; AMG = amygdala; FFG = fusiform gyrus; INS = insula; OC = occipital cortex; PC = parietal cortex; PCC = posterior cingulate gyrus.

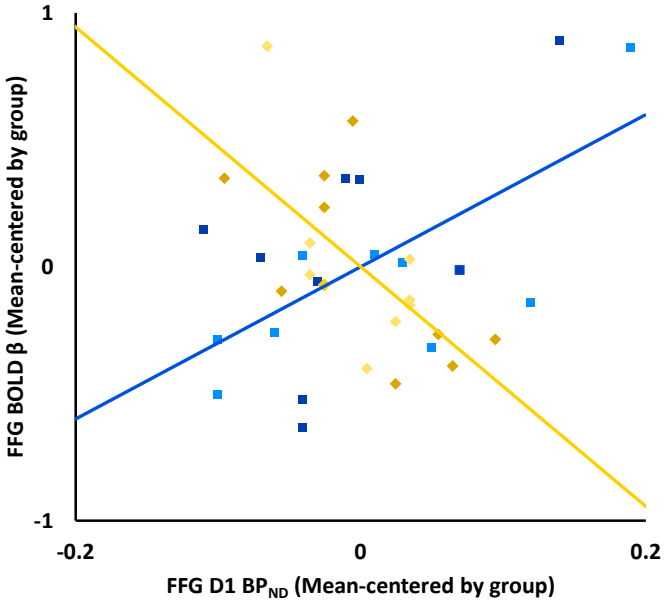

Fig. 4. BOLD in FFG as a function of D1 BP_{ND} in younger (blue squares) and older (yellow diamonds) groups. Colored lines represent least-squares regression lines. Younger adults' ($\beta = 0.13$, $r = 0.61$, $p = 0.007$) and older adults' ($\beta = -0.09$, $r = -0.65$, $p = 0.003$) D1 BP_{ND} predicted BOLD signal in opposite directions. Linear regression predicting BOLD from Group D1 BP_{ND} ratio revealed a significant main effect of D1 BP_{ND}, $F(1,32) = 19.20$ ($p < 0.001$). Further, a significant Group × D1 BP_{ND} interaction effect was observed, $F(1,32) = 19.07$ ($p < 0.001$). Within each group, better performers (those with d' scores equal to or above the median) are shaded darker, and worse performers (those with d' scores less than the median) are shaded lighter.

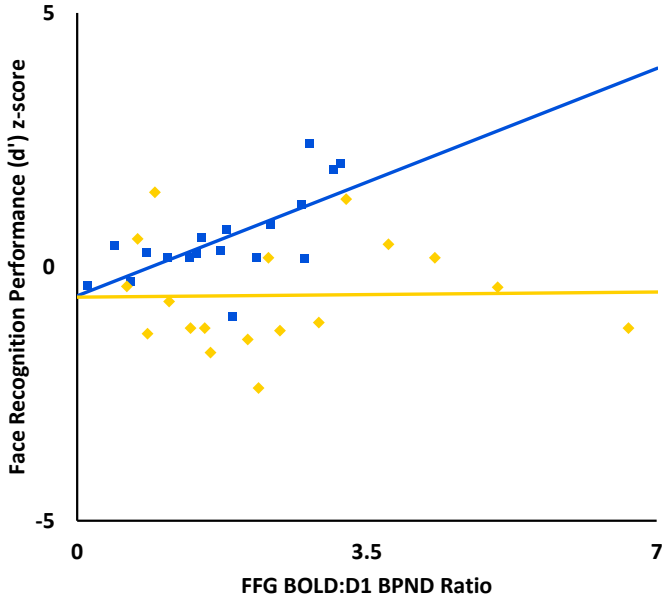

Fig. 5. Face recognition performance (d') as a function of the BOLD:D1 BP ratio in FFG, for younger (blue) and older (yellow) groups. Linear regression predicting *d*' from Group and BOLD:D1BP_{ND} ratio revealed a greater slope for younger ($\beta = 0.64$) than for older adults ($\beta = 0.01$), and a significant Group × BOLD:D1BP_{ND} Ratio interaction effect ($F = 5.36$, $p = 0.027$).

2011a; 2011b; Brehmer et al., 2011; Cools & D'Esposito, 2011; Landau et al., 2009; Nyberg et al., 2009; Rieckmann et al., 2011; Schott et al., 2008). Other studies (Bäckman et al., 2011a; Dreher et al., 2008; Li et al., 2013) have also found age-differences in DA-BOLD relationships. For instance, work by Dreher et al. (2008) demonstrated opposing relationships between midbrain DA levels and prefrontal cortex BOLD signal for younger and older adults during performance of a monetary incentive-delay task. The current finding of opposite DA-BOLD relationships between younger and older adults in FFG extends these observations to the face-recognition domain.

The age-differential relationship between neurotransmitter (DA) and hemodynamic (BOLD) systems was unique to FFG. Conceivably, the specificity of the result to this region reflects the dependence of the task on face-processing. FFG is activated during both encoding and recognition of facial stimuli (Grill-Spector et al., 2004; Henson et al., 2003; Kanwisher et al., 1997). However, DA-BOLD associations might exist in other areas that comprise the face processing network in more complex tasks. For instance, a task that involves judgments of facial attractiveness might also show a strong relationship between BOLD signal and D1 BP_{ND} in medial orbitofrontal cortex (O'Doherty et al., 2003) and nucleus accumbens (Cloutier et al., 2008), although combined fMRI-PET studies would be needed to test this hypothesis. Similarly, the DA-BOLD association might be strongest in amygdala while participants determine the

emotional state that a face exhibits (e.g., Adolphs, 2008; Wright et al., 2008). Studies focused on amygdala have shown results consistent with those observed here, through the use of fMRI (Bergman et al., 2014; Tessitore et al., 2002), PET (Bergman et al., 2014), and pharmacologic manipulations (Hariri et al., 2002; Takahashi et al., 2005). The consistency of our results with those of other studies that examine multiple brain regions and cognitive domains suggests brain-wide synchronization between neurotransmitter and hemodynamic systems that is vital to optimal neural and cognitive function, and that is adversely affected in aging.

The current results indicate that reduced D1 receptor availability influences the magnitude of the BOLD response. While we observed equivalent BOLD signal between age groups, the nature of the DA-BOLD relationship differed significantly between groups. Younger individuals with lower D1 BP_{ND} had lower task-related BOLD response compared to those with higher D1 receptor availability, whereas older adults showed the opposite DA-BOLD relationship. The DA-BOLD relationship observed in younger adults is consistent with murine models of DA-BOLD associations that have linked D1 receptor antagonism to lower BOLD signal (e.g., Choi et al., 2006). A positive linear relationship between BOLD and D1 BP_{ND} (such as we observed in younger adults) indicates synchronization between the two systems. In this system, higher BOLD signal is afforded by higher D1 receptor availability. We hypothesize that deviations from this positive linear relationship, such as we observed in older adults, indicate desynchronization between the two systems.

We hypothesize that age-related DA-BOLD desynchronization has consequences for face-recognition performance. Indeed, we observed age-differential relationships between the BOLD:D1 BP_{ND} ratio and task performance, as indicated by a significant Group × BOLD:D1BP_{ND} Ratio interaction effect on face-recognition accuracy. In younger adults, higher BOLD:D1 BP_{ND} ratio was associated with better face-recognition, but no such relationship was observed in older adults. Intact synchronization, as seen in younger adults, between DA and BOLD should permit tight coupling of neural activity to vascular activity. Conversely, desynchronization of neurotransmitter and hemodynamic systems could disrupt the timing of neural-hemodynamic coupling, resulting in suboptimal neural function, altered BOLD signal, and reduced performance (e.g., Abdelkarim et al., 2019; Arnsten, 1998; Arnsten and Goldman-Rakic, 1985; Arnsten et al., 1994; Hutchison et al., 2012, 2013; Tarantini et al., 2017).

Given that desynchronized neural-vascular activity could disrupt episodic face memory, it is of note that work by Li et al. (2013) demonstrates that age-related reductions in memory performance accompany changes to parameters of the sigmoidal relationship between neuronal input and firing probability. According to this view, synchrony between neurotransmitter and hemodynamic systems, such as we hypothesize occurs in healthy younger adults, could optimize the gain parameter of the sigmoidal function relating DA input to BOLD activation, resulting in more distinct memory representations and improved performance (Li et al., 2001, 2006a; 2006b, 2009; 2013; Nyberg et al., 2012; Rypma & D'Esposito, 2001; Servan-Schreiber et al., 1990). Desynchronized DA-BOLD activity, such as we hypothesize occurs in older adults, could result in reductions in the gain parameter, less distinct memory representations, and reduced face recognition performance relative to younger adults. Care must be taken, however, in drawing this conclusion, because the present analyses were informed by those we used in an earlier study involving only the young sample (Rypma et al., 2015). Additionally, work examining receptor selectivity of the radioligand used here (SCH23390) in non-human primates has found that up to one quarter of radioligand binding is actually not to D1 receptors at all, but in fact to 5-HT_{2A} receptors (Ekelund et al., 2007). Replication of these results in longitudinal studies with larger samples is certainly necessary to establish the reliability of the phenomena we observed here.

Performance on a wide variety of tasks, including episodic memory, working memory, and fluid intelligence, deteriorates in old age. Additionally, DA neurotransmission is altered in aging, as evidenced by decreasing D1 (Karrer et al., 2017; Rieckmann et al., 2011; Rinne et al., 1990; Suhara et al., 1991; Wang et al., 1998) and D2 (Inoue et al., 2001; Iyo et al., 1993; Kaasinen et al., 2000; Kaasinen and Rinne, 2002; Nyberg et al., 2016; Rinne et al., 1993) receptor availability, as well as the DA transporter involved in reuptake from the synapse (Karrer et al., 2017; Lavalaye et al., 2000; van Dyck et al., 1995, 2002; Volkow et al., 1994). Desynchronization between neurotransmitter and hemodynamic systems in older adults has been observed in murine studies examining DA-BOLD relationships in striatum (Choi et al., 2006; Knutson and Gibbs, 2007). Although the magnitude of the BOLD signal could influence DA release (Grace et al., 2007), striatal DA release more probably triggers activation of DA receptors, leading to increased BOLD signal, at least among younger adults (Roffman et al., 2016). Age differences in the strength of the DA-BOLD relationship observed here advance our understanding of age changes in the neural systems underlying cognition.

5. Conclusion

DA and BOLD in FFG exhibit a positive relationship in younger adults, while exhibiting an inverse relationship in older adults. A strong association exists between the BOLD:D1 BP_{ND} ratio in FFG and face-recognition performance, but only in younger adults. These results suggest that optimal DA-system function is critical to face processing. To the extent that DA and BOLD become uncoupled in aging, face recognition ability is compromised.

Authors' contributions

MT, HF, DS, NH, AR, BR, and LB contributed to drafting of the manuscript. HF, AR, BR, and LB contributed to experimental design and data collection. MT, HF, and NH contributed to data analysis. MT, DS, BR, and LB contributed to interpretation of results.

Declaration of competing interest

MT, HF, DS, NH, AR, BR, and LB declare no competing financial interests.

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