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Structural integrity of the substantia nigra and subthalamic nucleus predicts flexibility of instrumental learning in older-age individuals

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ABSTRACT

Flexible instrumental learning is required to harness the appropriate behaviors to obtain rewards and to avoid punishments. The precise contribution of dopaminergic midbrain regions (substantia nigra/ventral tegmental area [SN/VTA]) to this form of behavioral adaptation remains unclear. Normal aging is associated with a variable loss of dopamine neurons in the SN/VTA. We therefore tested the relationship between flexible instrumental learning and midbrain structural integrity. We compared task performance on a probabilistic monetary go/no-go task, involving trial and error learning of: "go to win," "no-go to win," "go to avoid losing," and "no-go to avoid losing" in 42 healthy older adults to previous behavioral data from 47 younger adults. Quantitative structural magnetization transfer images were obtained to index regional structural integrity. On average, both some younger and some older participants demonstrated a behavioral asymmetry whereby they were better at learning to act for reward ("go to win" > "no-go to win"), but better at learning not to act to avoid punishment ("no-go to avoid losing" > "go to avoid losing"). Older, but not younger, participants with greater structural integrity of the SN/VTA and the adjacent subthalamic nucleus could overcome this asymmetry. We show that interindividual variability among healthy older adults of the structural integrity within the SN/VTA and subthalamic nucleus relates to effective acquisition of competing instrumental responses.

1. Introduction

To efficiently harvest reward and avoid punishment, humans need to learn appropriate instrumental responses (Dickinson and Balleine, 2002) (O'Doherty et al., 2004). Recent data suggest that this basic form of behavioral adaptation is surprisingly inflexible in humans (Guitart-Masip et al., 2012b). Although healthy young human adults readily learn to act to obtain a reward, or not to act to avoid a punishment, they have difficulties learning to act to avoid a punishment and not to act to obtain a reward (Guitart-Masip et al., 2012b). This inflexibility in learning suggests that signals that predict rewards are prepotently associated with behavioral activation promoting approach behavior, whereas signals associated with punishments are intrinsically coupled to behavioral inhibition promoting avoidance. These behavioral tendencies can be described as Pavlovian biases that corrupt the flexibility of instrumental learning (Dayan et al., 2006; Gray and McNaughton, 2000). Computational modeling in young adults has shown that the observed pattern of behavior is captured by a model incorporating a Pavlovian bias, where the strength of this bias is related to failure to learn the conflicting conditions: no-go to win and go to avoid losing (Guitart-Masip et al., 2012b).

The substantia nigra/ventral tegmental area (SN/VTA) of the midbrain, the origin of dopaminergic projections, is important for instrumental learning (Salamone et al., 2005; Schultz et al., 1997) including signaling reward predictions errors (Schultz et al., 1997), energizing actions (Niv et al., 2007), and driving novelty-related exploratory behavior (Duzel et al., 2010; Lisman et al., 2011). In humans, dopaminergic medication after learning influences the brain responses to action and to reward anticipation (Guitart-Masip et al., 2012a). Importantly, the SN/VTA undergoes degeneration with aging (Bäckman et al., 2006; Fearnley and Lees, 1991; Vaillancourt et al., 2012). Age differences in instrumental learning have been linked to functional activity in dopaminergic target regions, including the striatum and prefrontal cortex (Samanez-Larkin et al., 2010) (Mell et al., 2009) (Fera et al., 2005)

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(Aizenstein et al., 2006). Structural degeneration of the SN/VTA and associated circuits can be indexed in vivo by magnetization transfer (MT) imaging, in which lower MT values reflect decreased structural integrity (Düzel et al., 2008; Eckert et al., 2004; Tambasco et al., 2011).

The goal of this study was to relate individual differences of SN/VTA integrity in older age to flexible instrumental learning for competing responses ("to act" or "not to act") to rewards and punishments. Furthermore, to explore age-group comparisons of learning and structural integrity of SN/VTA, we obtained separate data from younger adults. We hypothesized that older adults with higher SN/VTA integrity would show greater learning flexibility. Thus, instrumentally learning to act to avoid a punishment and not to act to obtain a reward would be equivalent to learning to act to obtain a reward or not to act to avoid a punishment, the latter being Pavlovian response biases that tend to dominate learning. We also obtained trait measures of novelty seeking in older adults to test the relationship with instrumental learning and structural integrity.

2. Methods

2.1. Participants

2.1.1. Older participants

A total of 42 healthy older adults aged 64 to 75 years (mean = 69.12 years. SD = 3.44 years; 29 females and 13 male, 40 right-handed and 2 left-handed) were recruited via our departmental Web site, advertisement in local public buildings, and word of mouth. Individuals were initially screened by telephone and excluded if they had any of the following: current or past history of neurological, psychiatric, or endocrinological disorders; metallic implants, tinnitus; major visual impairment; or history of drug dependency. To control for vascular risk factors, individuals known to have had a stroke or transient ischemic attack, myocardial infarction or other significant cardiovascular history, diabetes mellitus or hypertension requiring more than 1 antihypertensive medication were not eligible for participation. All participants undertook a neuropsychological test battery to ensure intact global cognitive performance (Supplementary Table 1). On the basis of this, no participants were excluded from the analysis (all participants scored within 1.5 SDs of the age-related norm for each test). All participants had a normal neurological examination (performed by a physician [R.C.]) ensuring that participants did not have concurrent undiagnosed neurological conditions. MRI scans were visually inspected to ensure that no participants had severe white matter changes or other major lesions. Clinical examination, neuropsychological testing, the go/no-go task, and structural MRI scanning were all performed in a single 4-hour session. Written informed consent was obtained from all participants. The study received ethical approval from the North West London Research Ethics Committee 2.

2.1.2. Younger participants

Data from 2 previously published experiments performed at the host institution were obtained to enable separate age-comparisons of behavioral data and MRI data. In 1 study, behavioral data from 47 healthy young adults (28 female and 19 male; mean age = 23.1 years, SD = 4.1 years) performing the same go/no-go task was obtained allowing comparisons of behavioral performance between young and older adults (Guitart-Masip, et al., 2012b). Structural neuroimaging including MT imaging was available for 30 of these younger adults, which we used to examine the correlation between SN/VTA integrity and task performance in younger adults. These scans were obtained on a different MRI scanner (3-T Siemens Allegra) using a different acquisition protocol that did not include B1 correction (Guitart-Masip, et al., 2012b for details), thus direct age-comparisons of actual MT values could not be made with this dataset and ours.

Therefore in the second study, neuroimaging data from 12 healthy younger adults (6 female and 6 male; mean age = 33.8 years, SD = 12.84 years), using the same MRI scanner and imaging sequence, was obtained to allow comparison of MT values of SN/VTA between younger and older adults (Lambert et al., 2012 for details).

2.2. Go/no-go task

Participants performed a probabilistic monetary go/no-go task as described in Guitart-Masip et al. (Guitart-Masip et al., 2012b) (Fig. 1). The correct response (to execute or withhold an action) to 4 cues (abstract fractal images) had to be learned through trial and error, to win or to avoid losing money. Participants were told that at the start of the task they would not know the correct responses (to press or not to press a button) for each image, but that these would become clear through trial and error. After seeing an image (1000 ms), there was a variable interval (250–2000 ms) after which participants were presented with a circle (target detection, 1500 ms), at which point they had to either press a button (go) with their dominant hand to indicate the target side within 1000 ms or not press a button (no-go). After this, the outcome was depicted for 1000 ms by a green up-pointing arrow (indicating a win of £1), a red down-pointing arrow (indicating a loss of £1), or a yellow horizontal bar (neither win nor lose). The outcome was probabilistic,

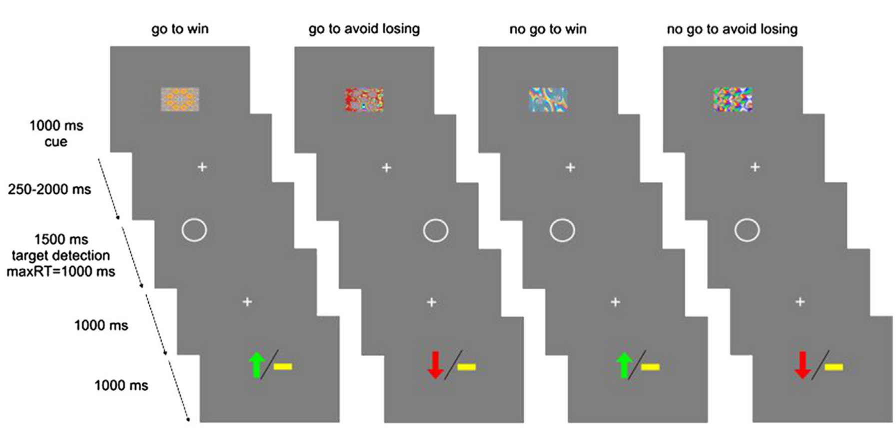

Fig. 1. Probabilistic monetary go/no-go task.