ORIGINAL ARTICLE

Probabilistic Tractography Between Nucleus Accumbens and Other Reward-related Brain Areas in Malay Female Adolescents

Siti Hajar Zabri[1,3], Asma Hayati Ahmad[2,3], Rahimah Zakaria[2], Aimi Nadhiah Abdullah[2], Siti Fatimah Mukhtar[4], Jafri Malin Abdullah[1,3]

[1] Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[2] Department of Physiology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[3] Brain & Behaviour Cluster, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[4] Department of Anatomy, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.

ABSTRACT

Introduction: Studies show that adolescents are more reward sensitive compared to other age groups. The nucleus accumbens (NAcc) has been identified as a key brain area involved in reward through its connectivity to other reward-related brain areas. Our study aimed to characterise the white matter structural connectivity of nucleus accumbens with brain areas that are most often associated with reward in female adolescents. **Methods:** Fifteen healthy female Malay adolescents were recruited and underwent diffusion-weighted brain scanning. Two behaviour scales were also given to verify typical reward responsiveness. Then, probabilistic tractography and NAcc segmentation were performed on the data using FMRIB Software Library (FSL). Probabilistic tractography was performed to determine the relative connection probability of nucleus accumbens (NAcc) to areas shown to be associated with reward, namely amygdala, anterior cingulate cortex (ACC), medial orbitofrontal cortex (mOFC), hippocampus, ventrolateral prefrontal cortex (vlPFC) and dorsolateral prefrontal cortex (dlPFC). Connectivity-based segmentation of NAcc was performed to determine the spatial distribution of its connectivity with the target brain areas according to the highest connection probability. **Results:** The highest relative connection probability was found between NAcc to mOFC, while the NAcc parcellation showed the widest distribution of connection to mOFC compared to the other five targets on both sides of the brain. **Conclusion:** Our findings demonstrated the strongest structural connectivity and widest distribution between NAcc and mOFC compared with other brain areas related to reward. This study's findings could be used as baseline to compare with people with atypical reward circuit problems.
Malaysian Journal of Medicine and Health Sciences (2023) 19(2):61-68. doi:10.47836/mjmhs19.2.11

Keywords: Nucleus accumbens, Medial orbitofrontal cortex, Reward, Diffusion MRI, Probabilistic tractography

Corresponding Author:
Asma Hayati Ahmad, PhD
Email: asmakck@usm.my
Tel: +609-7673000 ext. 6163

INTRODUCTION

Adolescents, defined as being in the age range of 10 to 25 years of age, are known to be associated with higher risk-taking behaviour and impulsivity (1–3). The adolescence period is commonly associated with the onset of substance abuse activity (4–6). This may be due to the constant development of brain regions during this period (2,7). Adolescents have also been shown to have higher reward sensitivity compared to other age groups (8,9). Reward sensitivity is a trait of temperament and personality with a considerable individual difference in the tendency to recognise, pursue, learn from, and receive pleasure from positive stimuli (10). Hence, the reward structural connectivity of this age group has previously been studied especially concerning reward sensitivity and addiction.

From previous studies of reward structural connectivity, during the adolescence period, an atypical reward network has been implicated in the initiation of substance use (4–6) and regions related to impulsivity, reward sensitivity and addiction have been identified (11–13). The accumbofrontal tract which connects the nucleus accumbens (NAcc) and the orbitofrontal cortex (OFC) is often studied in relation to reward including reward hypersensitivity in adolescents (4,8,14). The NAcc has also been found to have a major role in the reward system and it is more activated when it comes to cues that signal potential rewards compared to cues that signal no reward.

Dopamine is the main neurotransmitter that plays an important role in the brain reward system (15). Dopamine originates from the ventral tegmental area and the mesolimbic dopamine pathways related to reward includes the ventral striatum, NAcc, lateral

hypothalamus, amygdala and hippocampus (15,16). Structures in the mesocortical dopamine pathway involved in reward are the OFC, prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) (5,17).

Diffusion MRI is an excellent tool for investigating brain white matter integrity and has been used to investigate reward structural connectivity of the adolescent brain (4,12,13). This MRI-based imaging technique can be used to obtain the three-dimensional orientation of the brain's white matter tracts measured voxel by voxel (18,19). Fractional anisotropy is the measured parameter in diffusion MRI that describes the degree of diffusivity of water molecules between 0 (isotropic or freely diffusible in all directions) and 1 (diffusion is directional following the axis of the axon). Probabilistic tractography is a dMRI analysis technique that allows the reconstruction of tracts within the brain based on water diffusivity (20,21). Connection probability between areas in the brain, designated as seed and target, is obtained by tracking a set number of samples from the seed area and measuring how many of the samples reach the target (22). The advantage of this technique is that it provides a quantitative measurement of white matter connectivity in the form of connection probability.

It is not clear how the NAcc, a key structure in the modulation of reward, connects to six other reward-related regions which are the amygdala, ACC, medial orbitofrontal cortex (mOFC), hippocampus, ventrolateral prefrontal cortex (vlPFC) and dorsolateral prefrontal cortex (dlPFC). We hypothesized that the relative connection probability and parcellation of the NAcc to the six reward-related target regions would show the highest connection probability hence strongest connectivity to the medial orbitofrontal cortex (mOFC) compared to the other regions based on findings involving different study subjects (8,11,12,23). Thus, the objective of this study was to determine the relative connection probability and distribution of connection of the NAcc to six pre-determined targets in young healthy Malay female adolescents. The current study analysed only female adolescents because previous studies have found significant sex differences between male and female white matter microstructure (8,14,24). An example is the study by Karslgodt and colleagues where they found a significant sex difference of the age-related change in FA of the tract connecting NAcc to OFC (8). They found that males' tract mature faster, with a higher and earlier peak at age 13.9(±6.85) during adolescence, while in females, peak of tract maturity was much later at the age of 18.6(±3.79) years.

MATERIALS AND METHODS

Participants

We used data from a previous diffusion MRI scanning, whereby there were 30 samples. From the process of elimination due to incomplete MRI data, left-handedness, gender and no reward responsiveness data, only fifteen females were analysed further. The fifteen undergraduate or diploma students between 18 to 24 years of age were recruited from the Health Campus, Universiti Sains Malaysia. The inclusion criteria were right-handed females with normal colour vision and the ability to understand instructions in the MRI scanner. The exclusion criteria included the presence of contraindications to MRI scanning, history of psychiatric disorder requiring current psychotropic medication or previous inpatient psychiatric hospitalization, substance abuse, pregnancy, claustrophobia, and medications that may influence the central nervous system. Ethical approval was granted by the Human Research Ethics Committee of USM (JEPeM) (USM/JEPeM/20060295). Participants had also provided informed consent.

Psychological questionnaires

Participants were given online psychological tests, including the Reward Responsiveness scale (RRS) and the Behavioural Inhibition System and Behavioural Activation System (BIS/BAS) scale, to verify they exhibited typical reward responsiveness (25–28). RRS is able to measure reward responsiveness (28). An example of an item in the scale is "I am someone who goes all-out." The BIS/BAS scale measures two basic brain mechanism which is the behaviour inhibition system that is responsive to punishment and behavioural activation system that can assess sensitivity to reward (27,29). An example of an item in the scale is "It would excite me to win a contest." This information on reward responsiveness was compared to the typical scores of healthy teenagers in previous studies. Reward responsiveness items are shown to be related to reward sensitivity since they correlate with the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (28). Reward responsiveness however focuses more on reward rather than punishment.

Diffusion MRI data acquisition

The diffusion-weighted MRI data were acquired using Philips Achieva 1.5 Tesla in the year 2013. The parameters for DTI were: field of view (FOV) = 240 mm^2; b-value = 1000 s/mm^2, voxel resolution = 2.5 x 2.5 x 2.5 mm; number of slices = 67; slice thickness = 2.3 mm; repetition time (TR) = 10726 ms; echo time (TE) = 76 ms in 32 non-collinear diffusion directions with one b value = 0 mm/s2 image. High-resolution T1-weighted anatomical images using a 3D magnetized-prepared rapid gradient-echo (MPRAGE) were acquired with the following parameters: FOV, 256 mm^2, voxel resolution = 1 x 1 x 1 mm TR = 7.84 ms; TE = 3.86 ms, average number of slices = 170.4 (including 150, 160 and 176); slice thickness = 2 mm; inversion time = 900 ms; flip angle = 8^0.

Diffusion MRI data processing

Acquired data were processed using the FMRIB Software Library (FSL) software (www.fmrib.ox.ac.uk/fsl; Analysis

Group, FMRIB, Oxford, United Kingdom) (19,30,31). Firstly, the raw data were converted from DICOM to NIfTI using MRIConvert version 2.1.0. After conversion, the data can be further processed using the FMRIB Software Library (FLS) version six (19,31,32). Then, FMRIB Diffusion Toolbox (FDT) version five was used for eddy current correction. The images at b-value 0 was extracted from the diffusion-weighted images of each subject. This step was followed by the brain extraction step which was done for both 3D T1-weighted MRI image and no diffusion image. The brain extraction tool (BET) in FSL was used to obtain an image that excluded non-brain regions and generated a brain mask for further use in the subsequent steps (1,33,34). Automated modelling of crossing fibres was performed using bedpostX with the following parameters: number of fibre orientations per voxel = 2, weight = 1, and burn in = 1,000. This step produced the bedpostX output directory. This step was followed by the registration step to produce a set of transformation matrix files needed for tractography since the masks in this study are in standard space (not in diffusion space). So, the two transformation matrices which were standard to diffusion and diffusion to standard (non-linear transform) were needed.

In the registration step, the no diffusion image which was extracted using BET tool was first put into the bedpostX output directory. Brain extracted structural image was put into the directory with default setting: normal search, six degrees of freedom (DOF) and correlation ratio. The original T1 weighted image which included non-brain regions was then chosen. Lastly, standard space of T1 weighted image of Montreal Neurosciences Institute (MNI152) 1mm brain was chosen with default settings: normal search, 12 DOF and correlation ratio.

Regions of Interest

The regions of interest (ROI) were defined on the T1-weighted images for each subject using the FSLeyes package (within FSL software). The anatomical landmarks were determined using the Harvard-Oxford atlas provided. The nucleus accumbens (NAcc) was selected as the seed region while the target regions included the amygdala, ACC, mOFC, hippocampus, vlPFC and dlPFC as determined from previous studies on reward network (11,12,23). The Harvard-Oxford atlas was used for all the ROIs with specific thresholds set for each ROI. The NAcc was thresholded at 40% while amygdala, ACC, mOFC, hippocampus, vlPFC and dlPFC were thresholded at 50%, 25%, 20%, 50%, 30% and 20% respectively. An example of masks set for the ROIs is shown in Fig. 1.

Probabilistic tractography

Probabilistic tractography was performed from the NAcc to six pre-determined target structures: amygdala, ACC, mOFC, hippocampus, vlPFC, and dlPFC to determine the connection probability of NAcc to the six reward-related brain regions. The bedpostX datasets were used

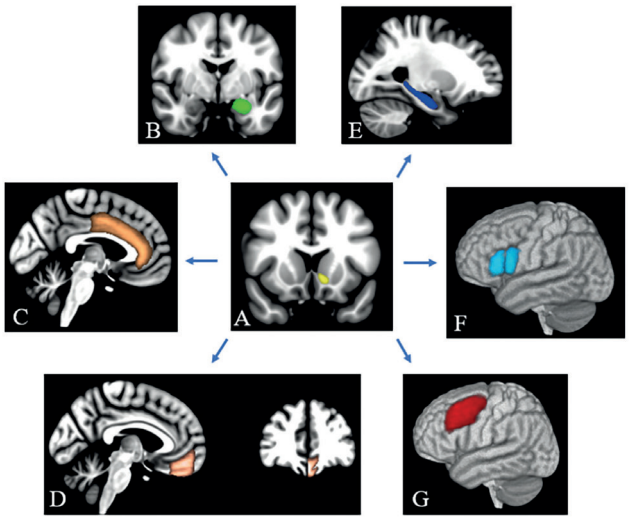

Fig. 1: Examples of the seed (A) and the subcortical (B,E) and cortical (C,D,F,G) target masks on the left hemisphere. Masks were derived from FSLeyes which was then used for probabilistic tractography from the nucleus accumbens to each target. (A) Nucleus accumbens, NAcc (B) Amygdala; (C) Anterior cingulate cortex, ACC; (D) Medial orbitofrontal cortex (mOFC); (E) Hippocampus; (F) Ventrolateral prefrontal cortex, vlPFC (G) Dorsolateral prefrontal cortex, dlPFC

to run probtrackX, a part of FDT (14,19,32). From each voxel in the NAcc, 5000 samples were generated and used to track to all the targets. The FSL default was set which includes 0.2 for curvature threshold and loop check termination.

The quantitative analysis was performed for each subject from the connection probability output produced from the tracking (34). It is indicative of the probability that there is a connection between the seed area and target. From the 5000 samples initiated from each voxel within the NAcc seed region, the number of streamlines was determined whereby streamline is equal to mean (M) times volume (V). M represents the mean number of samples per voxel within a seed area with a positive connection probability to the target while V represents the number of voxels in the seed area with a positive connection probability to the target. The assumption is that stronger white matter connectivity between the seed and target areas will be shown by a higher number of streamlines (22,35,36). The percentage of relative connection probability was then calculated for each subject on both the left and right hemisphere. Relative connection probability (RCP) is the percentage of connection probability of the seed to each target over the total connection probability of the seed to all the six targets (22,37). The mean relative connection probability was then calculated to obtain the average RCP within the group.

$$RCP = (MiVi/\Sigma MV) \times 100$$

The relative connection probability was averaged over all NAcc voxels, and this value was then averaged

across all 15 subjects.

Parcellation of NAcc

Connectivity-based parcellation of NAcc was done via FSLeyes for each participant. The images were focused specifically on the NAcc region for easier visualization. The FSL file labelled "biggest" obtained from the previous probtrackX step was opened whereby hard clustering was applied to the tractography result. This displayed the segmentation of NAcc into six clusters which corresponded to the probabilistic connectivity pattern to each of the six target masks. This clustering method assigned each voxel within the NAcc to the target with the highest connection probability (38,39).

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 26 was used for the descriptive analysis of demographic data and questionnaires.

RESULTS

Characteristics and psychological scores

The characteristics and psychological scores of the participants are summarised in Table I. The mean age for the participants was 19.47 (±0.64) and ranged from 18 to 20 years old. The mean reward responsiveness score (RRS), Behavioural Inhibition System (BIS) score, Behavioural Activation System (BAS) reward responsive score, BAS drive score and BAS fun seeking score for the participants were 24.07 (±2.81), 22.40 (±2.23), 18.60 (±1.76), 13.27 (±1.83) and 12.13 (±1.36), respectively.

Relative connection probability

Probabilistic tractography performed from the NAcc to six pre-determined target structures: amygdala, ACC, mOFC, hippocampus, vlPFC, and dlPFC showed that the NAcc had the highest probability of connection with the mOFC relative to other targets for both hemispheres (Fig. 2 and Fig. 3). The average relative connection probability from NAcc to the six target regions; amygdala, ACC, mOFC, hippocampus, vlPFC, and dlPFC was 14.6%, 6.5%, 65.2%, 10.9%, 1.4% and 1.5% respectively in the left hemisphere. In comparison, the average relative connection probability from NAcc to mOFC was 4.4 to 48.2 times higher than the average relative connection probabilities to the other five target regions.

In the right hemisphere, the average relative connection probability from NAcc to the six target areas; amygdala, ACC, mOFC, hippocampus, vlPFC, and dlPFC was 8.7%, 15.9%, 64.9%, 5.3%, 3.1% and 2.1% respectively. The average relative connection probability between NAcc and mOFC was 4.1 to 30.9 times higher compared to the relative connection probabilities of the other five target areas. There was also no overlap between the standard error of mean (SEM) error bars of NAcc to mOFC relative connection probability with the error bars of the other target regions, indicative of statistical significance as it was calculated with the same sample size.

Table I: Characteristics, psychological scores of the participants and normal range

Variables	Mean (SD)	Range	Normal range (ref.)
Age (years)	19.47(0.64)	18-20	-
Weight (kg)	51.80 (10.84)	40-72	-
Height (cm)	155.00 (4.36)	149-164	-
RRS score	24.07 (2.81)	19-28	18-32 (26,41)
BIS score	22.40 (2.23)	19-26	10-28 (40,42-44)
BASRR score	18.60 (1.76)	15-20	9-20 (40,42-44)
BASD score	13.27 (1.83)	10-16	5-16 (40,42-44)
BASFS score	12.13 (1.36)	11-15	5-16 (40,42-44)

RRS: Reward Responsiveness Scale, BIS: Behavioural Inhibition System, BASRR: Behavioural Activation System Reward Responsiveness, BASD: Behavioural Activation System Drive and BASFS: Behavioural Activation System Fun Seeking.

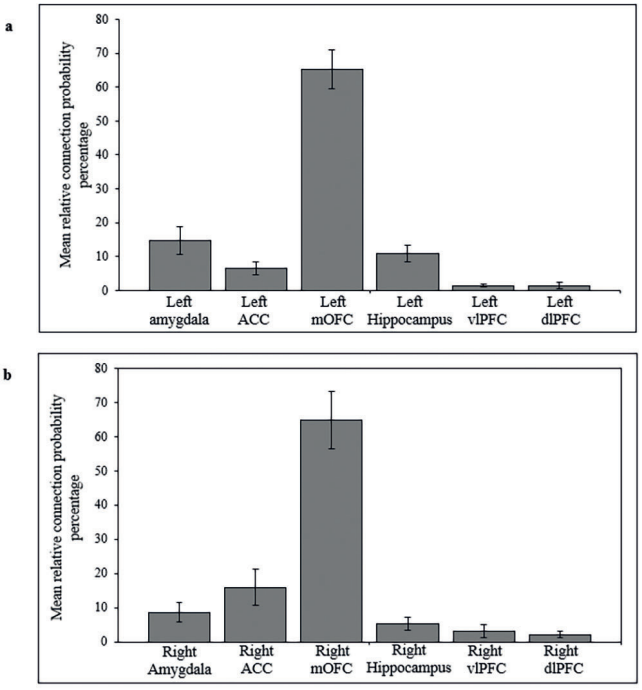

Fig. 2: Mean relative connection probability (%) between NAcc to the 6 reward-related regions in all 15 participants. ACC, anterior cingulate cortex; mOFC, medial orbitofrontal cortex; vlPFC, ventrolateral prefrontal cortex; dlPFC dorsolateral prefrontal cortex. a, left hemisphere b, right hemisphere

Individual analysis of the results showed that four participants differed from the group average (Fig 5-8). One participant (subject three) had the highest connection probability to the amygdala on the left hemisphere and the ACC on the right hemisphere. Two other participants (subject four and subject six) had the highest relative connection probability to the amygdala on the right hemisphere while another participant (subject eight) showed the highest relative connection probability to the ACC on the right hemisphere. These three latter participants all had the highest relative connection probability to the mOFC in the left hemisphere.

Parcellation of NAcc

The wide distribution of connectivity to the mOFC

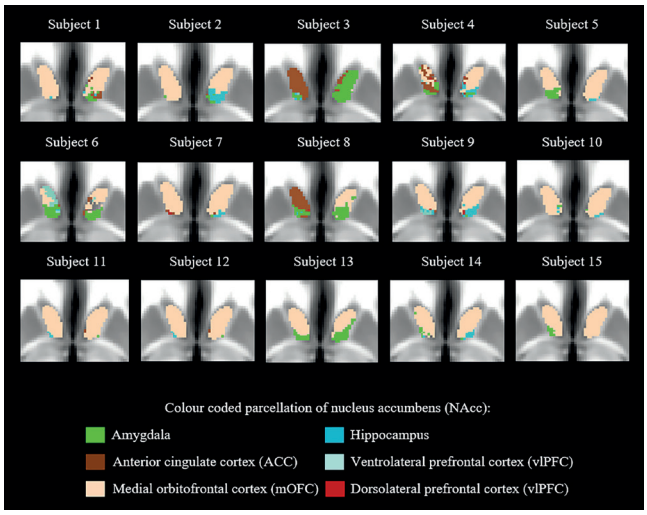

Fig. 3: Connectivity-based segmentation of nucleus accumbens (NAcc) and corresponding six reward-related target regions colour-coded by region. Each voxel in the NAcc is labelled according to the target region with which the connection probability was highest.

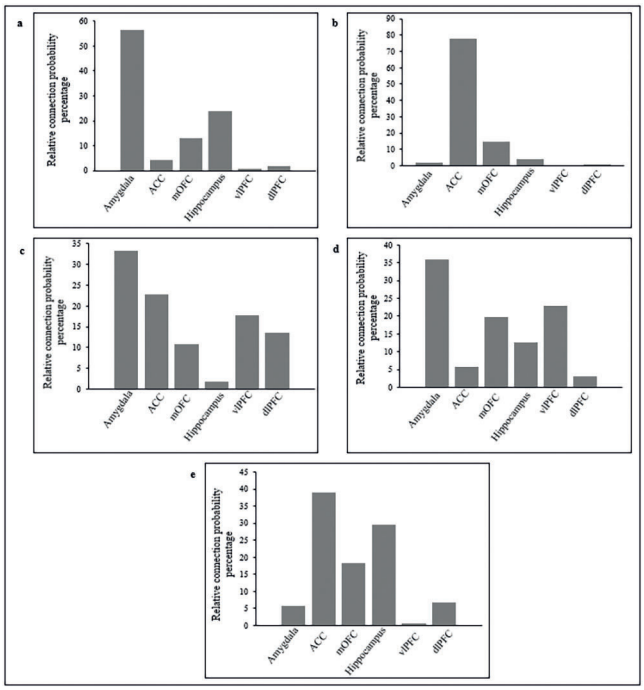

Fig. 4: Relative connection probability (%) between NAcc to the six reward-related regions in outlier subjects. ACC, anterior cingulate cortex; mOFC, medial orbitofrontal cortex; vlPFC, ventrolateral prefrontal cortex; dlPFC dorsolateral prefrontal cortex. a, Relative connection probability (%) of subject 3 in the left hemisphere. Relative connection probability values are 56.3%, 4.3%, 13.1%, 23.9%, 0.7% and 1.6% respectively. b, Relative connection probability (%) of subject 3 in the right hemisphere. Relative connection probability values are 1.9%, 77.9%, 14.9%, 4.1%, 0.5% and 0.6% respectively. c, Relative connection probability (%) of subject 4 in the right hemisphere. Relative connection probability values are 33.2%, 22.8%, 10.9%, 1.9%, 17.7% and 13.5% respectively. d, Relative connection probability (%) of subject 6 in the right hemisphere. Relative connection probability values are 35.9%, 5.7%, 19.7%, 12.7%, 22.9% and 3.1% respectively. e, Relative connection probability (%) of subject 8 in the right hemisphere. Relative connection probability values are 5.7%, 39.1%, 18.4%, 29.4%, 0.6% and 6.8% respectively

shown on the NAcc further supports that the NAcc-mOFC had the highest relative connection probability for the majority of the participants for both right and left hemisphere. The distribution pattern of the mOFC connectivity was shown to cover a wider surface of the NAcc seed region compared to the connections with the other five target regions for most of the participants as shown in Fig. 4.

DISCUSSION

Our study aimed to characterise the structural connectivity between NAcc, an area identified to be involved in reward, with other brain areas previously shown to be implicated with reward processing, in healthy Malay female adolescents (11,12,23). The scores on the Reward Responsiveness scale and the BIS/BAS scale showed that all the participants scored within the normal range of typical reward responsiveness as indicated by previous studies (26,40–44).

The relative connection probability of NAcc and mOFC was shown to be highest compared to that of NAcc to the amygdala, ACC, hippocampus, vlPFC and dlPFC on both left and right hemispheres. This was also supported by the parcellation result. Similarly, the tract connecting NAcc and the OFC, the accumbofrontal tract, was characterised by Karlsgodt et. al, (2015) in their diffusion tensor imaging study of healthy individuals aged 8-68 (8). Even though the terminal tractography ROI did include the whole region of the orbitofrontal cortex, the connection was limited to only the medial region of the white matter (8). Hence, mOFC was chosen as the target in our study and many studies that focus on the NAcc-mOFC tract for reward-related research (1,8,14).

The findings of the current study that the tract has a very high relative connection strength between NAcc and mOFC may be attributed to the early maturity of the accumbofrontal tract. Karlsgodt et. al, (2015) showed that the accumbofrontal tract matured around mid-adolescence. The average fractional anisotropy (FA) in the accumbofrontal tract undergoes significant changes with age across the lifespan whereby there is an early peak at the age of 14.8 (1.76) followed by a decrease and then levelled out. In addition, they found a sex difference whereby the accumbofrontal tract of males matures earlier at the age of 13.9 (6.85) compared to females at the age of 18.6 (3.79). Van den Bos et. al, (2015) investigated adolescents at the age of 18 to 25 and found that striatum showed increased connectivity with age to dlPFC, ACC, and amygdala but not to mOFC, the left vlPFC, and the hippocampus (12). The NAcc is the central hub in the reward circuit (16,45) and is a region for integration of emotional and cognitive input for modulating goal-directed behaviour (16,45,46). The mOFC is important in reward valuation in both anticipation and consummation (47–49). A previous human study found that mOFC lesions affected the ratings on choice-free valuation and even decreases

self-control during an intertemporal choice task. This task requires the participants to choose between a more immediate reward that is smaller in value or the postponed reward that has a much larger value (48). This suggests that mOFC damage increases the impulsivity of participants. If future studies were to look into the abnormal or non-typical reward network of participants, it may show less connection strength of this tract. This was found by Yuan and colleagues whereby the tract strength of NAcc-mOFC was significantly weaker in smokers compared to non-smokers (23).

Irregularities of the reward network may be the explanation for the tendencies of adolescents to adopt risky behaviours and make suboptimal decisions. Adolescents' prefrontal cortex continue to develop into early adulthood while having a mature limbic system (2,7). Hence, adolescents have been shown to be more biased toward reward evaluation by the limbic system compared to the prefrontal system. Previous studies have found that the complete development of the adolescents' prefrontal cortex is near the age of 25 (33,50). Hence, even though the accumbofrontal tract matures early, the prefrontal cortex is one of the last brain regions to reach maturation and is not completely matured until near the age of 25 (33,50). The prefrontal cortex in general also plays a major role in the regulation of behaviour (33). This means that even if the adolescents understand that something is dangerous, with an immature prefrontal cortex, they may still be engaging in risky behaviour (33,50). Previous work had found that reward and executive functions do not mature alongside each other with existing behavioural evidence showing that reward network matures earlier which leads to a higher reward sensitivity or stronger motivation for seeking out opportunities perceived as rewarding (8). On the other hand, the brain regions for cognitive control or the executive network were found to mature much slower leaving the adolescents with a lower ability for behaviour regulation. (8,33,50).

The current study found individual differences compared to the group majority on the strongest connectivity of NAcc to the targets as shown by four subjects. These findings showed that there was individual variation within the group. However, our analysis did not allow for individual exploration due to its small sample. It should be noted that the scores of the four participants obtained for both RRS and BIS/BAS were still of typical reward responsiveness of healthy participants.

The limitation of this study is that the results could not be generalized to the Malay male adolescents because only females were analysed in this study. Other than that, the reward responsiveness scales given to the patients, the RRS and the BIS/BAS scales to ensure that the sample had typical reward responsiveness scores of healthy participants for future studies to compare the data to those of addiction or having reward-related abnormalities. The normal range of reward responsive data obtained from the participants were taken from previous studies of other ethnicities which were a mix of Caucasian, African American, Asians, Latino and other ethnicities and not the data of previous Malay ethnicity (26,42–44). Some had mostly Caucasian participants. Furthermore, the behavioural data was taken 8 years after the diffusion MRI scan was taken.

Future studies should look into comparing this group finding of relative connection probability data and comparing with groups with addiction or other reward-related behavioural abnormalities. In addition, a longitudinal study of relative connection probability between the reward-related connectivity with similar seed and target mask in the current study can allow the analysis of the relative connection probability pattern throughout lifespan so that different age groups such as children, adolescents, adults and even elderly can be compared.

CONCLUSION

When compared to other reward-related brain regions, NAcc and mOFC had the strongest structural connection and the largest distribution within the NAcc segmentation for both left and right hemisphere. These study findings could be utilised as baseline data to compare persons who have unusual reward circuit disorders.

ACKNOWLEDGEMENTS

This study was funded by the Ministry of Higher Education (MOHE) Malaysia for Fundamental Research Grant Scheme (FRGS) with Project Code FRGS/1/2019/SKK03/USM/02/4.

REFERENCES

1. Ikuta T, del Arco A, Karlsgodt KH. White matter integrity in the fronto-striatal accumbofrontal tract predicts impulsivity. Brain Imaging Behav. 2018;12(5):1524–8. doi: 10.1007/s11682-017-9820-x.
2. Sawyer SM, Azzopardi PS, Wickremarathne D, Patton GC. The age of adolescence. Lancet Child Adolesc Heal. 2018;2(3):223–8. doi: 10.1016/S2352-4642(18)30022-1.
3. van Duijvenvoorde ACK, Peters S, Braams BR, Crone EA. What motivates adolescents? Neural responses to rewards and their influence on adolescents' risk taking, learning, and cognitive control. Neurosci Biobehav Rev. 2016;70:135–47. doi: 10.1016/j.neubiorev.2016.06.037.
4. Squeglia LM, Sorg SF, Jacobus J, Brumback T, Taylor CT, Tapert SF. Structural connectivity of neural reward networks in youth at risk for substance use disorders. Psychopharmacol. 2015;232(12):2217–

26. doi: 10.1007/s00213-014-3857-y.
5. Squeglia LM, Cservenka A. Adolescence and Drug Use Vulnerability: Findings from Neuroimaging. Curr Opin Behav Sci. 2017;13:164–70. doi: 10.1016/j.cobeha.2016.12.005.
6. Squeglia LM, Ball TM, Jacobus J, Brumback T, McKenna BS, Nguyen-Louie TT, et al. Neural predictors of initiating alcohol use during adolescence. Am J Psychiatry. 2017;174(2):172–85. doi: 10.1176/appi.ajp.2016.15121587.
7. Somerville LH. Searching for Signatures of Brain Maturity: What Are We Searching For? Neuron. 2016;92(6):1164–7. doi: 10.1016/j.neuron.2016.10.059.
8. Karlsgodt KH, John M, Ikuta T, Rigoard P, Peters BD, Derosse P, et al. The accumbofrontal tract: Diffusion tensor imaging characterization and developmental change from childhood to adulthood. Hum Brain Mapp. 2015;36(12):4954–63. doi: 10.1002/hbm.22989
9. Steinberg L, Icenogle G, Shulman EP, Breiner K, Chein J, Bacchini D, et al. Around the world, adolescence is a time of heightened sensation seeking and immature self-regulation. Dev Sci. 2018;21(2):1–13. doi: 10.1111/desc.12532.
10. Goodnight JA. The SAGE Encyclopedia of Lifespan Human Development. Thousand Oaks,: SAGE Publications, Inc.; 2018.
11. van den Bos W, Rodriguez CA, Schweitzer JB, Mcclure SM. Connectivity Strength of Dissociable Striatal Tracts Predict Individual Differences in Temporal Discounting. J Neurosci 2014;34(31):10298-310. doi: 10.1523/JNEUROSCI.4105-13.2014.
12. van den Bos W, Rodriguez CA, Schweitzer JB, Mcclure SM. Adolescent impatience decreases with increased frontostriatal connectivity. Proc Natl Acad Sci U S A 2015;112(29):E3765-74. doi: 10.1073/pnas.1423095112.
13. Yuan K, Zhao M, Yu D, Manza P, Volkow ND, Wang GJ, et al. Striato-cortical tracts predict 12-h abstinence-induced lapse in smokers. Neuropsychopharmacology. 2018;43(12):2452–8. doi: 10.1038/s41386-018-0182-x.
14. Damme KS, Young CB, Nusslock R. Elevated nucleus accumbens structural connectivity associated with proneness to hypomania: A reward hypersensitivity perspective. Soc Cogn Affect Neurosci. 2017;12(6):928–36. doi: 10.1093/scan/nsx017.
15. Gibson G. Cocaine and the Dopamine Hypothesis of Addiction FYS100C : Gotta Have It : Exploring the Science of Addiction. 2017; Chemistry: Student Scholarship & Creative Works. 7. https://jayscholar.etown.edu/chemstu/7
16. Haber SN. Anatomy and connectivity of the reward circuit. Decis Neurosci An Integr Perspect. 2017;3–19. doi: 10.1016/B978-0-12-374620-7.00001-7
17. Elliott BL, Blais C, McClure SM, Brewer GA. Neural correlates underlaying the effect of reward value on recognition memory. Neuroimage. 2020;206:1–10. doi: 10.1016/j.neuroimage.2019.116296
18. Leuze C, Goubran M, Barakovic M, Aswendt M, Tian Q, Hsueh B, et al. Comparison of diffusion MRI and CLARITY fiber orientation estimates in both gray and white matter regions of human and primate brain. Neuroimage. 2021;228:117692. doi: 10.1016/j.neuroimage.2020.117692
19. Meoded A, Orman G, Huisman TAGM. Diffusion Weighted and Diffusion Tensor MRI in Pediatric Neuroimaging Including Connectomics: Principles and Applications. Semin Pediatr Neurol. 2020;33:100797. doi: 10.1016/j.spen.2020.100797.
20. Mollink J, van Baarsen KM, Dederen PJWC, Foxley S, Miller KL, Jbabdi S, et al. Dentatorubrothalamic tract localization with postmortem MR diffusion tractography compared to histological 3D reconstruction. Brain Struct Funct. 2016;221(7):3487–501. doi: 10.1007/s00429-015-1115-7.
21. Caan MWA. DTI Analysis Methods: Fibre Tracking and Connectivity. In: Diffusion Tensor Imaging. 2016. https://radiologykey.com/dti-analysis-methods-fibre-tracking-and-connectivity/
22. Samsir S, Zakaria R, Abdul Razak S, Ismail MS, Abdul Rahim MZ, Lin CS, et al. Characterisation of the corticospinal tract using diffusion magnetic resonance imaging in unilateral and bilateral cerebral palsy patients. Malaysian J Med Sci. 2018;25(5):68–78. doi: 10.21315/mjms2018.25.5.7.
23. Yuan K, Yu D, Zhao M, Li M, Wang R, Li Y, et al. Abnormal frontostriatal tracts in young male tobacco smokers. Neuroimage. 2018;183:346–55. doi: 10.1016/j.neuroimage.2018.08.046.
24. Van Hemmen J, Saris IMJ, Cohen-Kettenis PT, Veltman DJ, Pouwels PJW, Bakker J. Sex Differences in White Matter Microstructure in the Human Brain Predominantly Reflect Differences in Sex Hormone Exposure. Cereb Cortex. 2017;27(5):2994–3001. doi: 10.1016/j.neuroimage.2018.08.046
25. Assari S, Boyce S, Akhlaghipour G, Bazargan M, Caldwell CH. Reward responsiveness in the adolescent brain cognitive development (ABCD) study: African Americans' diminished returns of parental education. Brain Sci. 2020;10(6):1–18. doi: 10.3390/brainsci10060391.
26. Atkinson J. Commonalities in the association of behavioral activation and behavioral inhibition with problem gambling and alcohol use in young adult college students. J Gambl Stud. 2018;35(1):125–41. doi: 10.1007/s10899-018-9788-5.
27. Carver CS, White TL. Behavioural Inhibition, Behavioural Activation, and Affective Responses to Impending Reward and Punishment: The BIS/BAS Scales. J Pers Soc Psychol. 1994;67(2):319–33.

doi: 10.1037/0022-3514.67.2.319
28. Van den Berg I, Franken IHA, Muris P. A new scale for measuring reward responsiveness. Front Psychol. 2010;1:239. doi:10.3389/fpsyg.2010.00239
29. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/ BAS scales. Journal of Personality and Social Psychology. 1994;67:319-333. doi: 10.1037/0022-3514.67.2.319
30. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23:208–19. doi: 10.1016/j.neuroimage.2004.07.051.
31. Wang C, Wang S, Huang P, Shen Z, Qian W, Luo X, et al. Abnormal white matter tracts of insula in smokers. Brain Imaging Behav. 2021;15(4):1955-1965. doi: 10.1007/s11682-020-00389-1.
32. Behrens T, Johansen-Berg H, Woolrich M, Smith S, Wheeler-Kingshott C, Boulby P, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci. 2003;6:750–757. doi: 10.1038/nn1075.
33. Demidenko MI, Huntley ED, Jahn A, Thomason ME, Monk CS, Keating DP. Cortical and subcortical response to the anticipation of reward in high and average/low risk-taking adolescents. Dev Cogn Neurosci. 2020;44:100798. doi: 10.1016/j.dcn.2020.100798
34. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp. 2002;17(3):43–155. doi: 10.1002/hbm.10062.
35. Jbabdi S, Johansen-berg H. Tractography : Where Do We Go from Here? Brain Connect..2011;1(3):169-83. doi: 10.1089/brain.2011.0033
36. Zorlu N, 3apraz N, Oztekin E, Bagci B, Di Biase MA, Zalesky A, et al. Rich club and reward network connectivity as endophenotypes for alcohol dependence: a diffusion tensor imaging study. Addict Biol. 2019;24(2):265–74. doi: 10.1111/adb.12599
37. Thanarajah SE, Han CE, Rotarska-Jagiela A, Singer W, Deichmann R, Maurer K, et al. Abnormal connectional fingerprint in schizophrenia: A novel network analysis of diffusion tensor imaging data. Front Psychiatry. 2016;7,114:1–10. doi: 10.3389/fpsyt.2016.00114
38. Reislev NH, Dyrby TB, Siebner HR, Lundell H, Ptito M, Kupers R. Thalamocortical Connectivity and Microstructural Changes in Congenital and Late Blindness. Neural Plast. 2017;2017:9807512. doi: 10.1155/2017/9807512
39. Osadchiy V, Labus JS, Gupta A, Jacobs J, Ashe-McNalley C, Hsiao EY, et al. Correlation of tryptophan metabolites with connectivity of extended central reward network in healthy subjects. PLoS One. 2018;13(8):1–16. doi: 10.1371/journal.pone.0201772
40. Umemoto A, Holroyd CB. Neural mechanisms of reward processing associated with depression-related personality traits. Clin Neurophysiol. 2017;128(7):1184–96. doi: 10.1016/j.clinph.2017.03.049.
41. Uro ević S, Collins P, Muetzel R, Lim K, Luciana M. Longitudinal changes in behavioral approach system sensitivity and brain structures involved in reward processing during adolescence. Dev Psychol. 2012;48:1488–1500. doi: 10.1037/a0027502.
42. Ameral V, Bishop LS, Palm Reed KM. Beyond symptom severity: The differential impact of distress tolerance and reward responsiveness on quality of life in depressed and non-depressed individuals. J Context Behav Sci. 2017;6(4):418–24. doi: 10.1016/j.jcbs.2017.08.004
43. Oumeziane BA, Jones O, Foti D. Neural Sensitivity to Social and Monetary Reward in Depression: Clarifying General and Domain-Specific Deficits. Front Behav Neurosci. 2019;13(199):1–16. doi: 10.3389/fnbeh.2019.00199
44. Linke J, Wessa M. Mental Imagery Training Increases Wanting of Rewards and Reward Sensitivity and Reduces Depressive Symptoms. Vol. 48, Behavior Therapy. Elsevier Ltd; 2017. 695–706 p. doi: 10.1016/j.beth.2017.04.002
45. Soares-Cunha C, de Vasconcelos NAP, Coimbra B, Domingues A, Silva JM, Loureiro-Campos E, et al. Nucleus accumbens medium spiny neurons subtypes signal both reward and aversion. Mol Psychiatry. 2020;25(12):3241–55. doi: 10.1038/s41380-019-0484-3
46. Floresco SB. The nucleus accumbens: An interface between cognition, emotion, and action. Annu Rev Psychol. 2015;66(1):25–32. doi: 10.1146/annurev-psych-010213-115159.
47. Wang Y, Ning M, Xiaosong H, Li N, Zhengde W, Lizhuang Y, et al. Neural substrates of updating the prediction through prediction errorduring decision making. Neuroimage. 2017;157:1–12. doi: 10.1016/j.neuroimage.2017.05.041.
48. Peters J, D'Esposito M. Effects of Medial Orbitofrontal Cortex Lesions on Self-Control in Intertemporal Choice. Curr Biol. 2016;26(19):2625–8. doi: 10.1016/j.cub.2016.07.035
49. Yan C, Su L, Wang Y, Xu T, Yin DZ, Fan MX, et al. Multivariate Neural Representations of Value during Reward Anticipation and Consummation in the Human Orbitofrontal Cortex. Sci Rep. 2016;6(29079):1–12. doi: 10.1038/srep29079.
50. Fryt J. Adolescent sensitivity to rewards, risk-taking, and adaptive behaviour: Development of the dual systems perspective. Postep Psychiatr i Neurol. 2017;26(3):140–5. doi: 10.5114/ppn.2017.70545