UNDERSTANDING THE BRAIN CONNECTIVITY OF REWARD NETWORK AMONG YOUTHS – A COMBINED fMRI-DTI STUDY

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by

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ACC	Anterior Cingulate Cortex
BET	Brain Extracting Tools
BOLD	Blood-oxygen-level-dependent
CPI	Connection probability index
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EEG	Electroencephalogram
EHI	Edinburgh Handedness Inventory
FDT	FMRIB Diffusion Toolbox
fMRI	Functional Magnetic Resonance Imaging
FMRIB	Functional MRI of the Brain
FWHM	Full-width half maximum
GLM	General linear model
HP-VTA	Hippocampus – ventral tegmental area
HRF	Hemodynamic response function
IFG	Inferior frontal gyrus
MFG	Middle frontal gyrus
MID	Monetary incentive delay
MNI	Montreal Neurological Institute
mOF	Medial orbito-frontal cortex
MOG	Middle occipital gyrus
mPFC	Medial prefrontal cortex
NAcc	Nucleus accumbens
OFC	Orbitofrontal cortex
PCC	Posterior cingulate cortex
PcGc	Posterior cingulum cortex
PET	Positron Emission Tractography
PFC	Prefrontal cortex
PPI	Psychophysiological interaction analysis

PrG	Precentral gyrus
ReML	Restricted Maximum Likelihood
RFX	Random effect analysis
ROI	Region of Interest
rsFMRI	Resting-state functional magnetic resonance imaging
RT	Reaction time
SD	Subthreshold depression
SEM	Standard error of the mean
SFG	Superior frontal gyrus
SID	Social incentive delay
SN	Substantia nigra
SOG	Superior occipital gyrus
SPSS	Statistical Package for the Social Sciences
STG	Superior temporal gyrus
tDCS	transcranial direct current stimulation
UF	Uncinate fasciculus
UNDESA	United Nations Department of Economic and Social Affairs
VLPFC	Ventrolateral prefrontal cortex
vmPFC	Ventromedial prefrontal cortex
VP	Ventral pallidum
VTA	Ventral tegmental area
WM	White matter

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MEMAHAMI KETERKAITAN OTAK DALAM RANGKAIAN GANJARAN DALAM KALANGAN BELIA – SATU GABUNGAN KAJIAN FMRI-DTI

ABSTRAK

Memahami rangkaian otak untuk ganjaran dalam kalangan belia boleh menjelaskan mekanisme asas yang mempengaruhi keputusan kehidupan yang penting. Kajian terdahulu telah menunjukkan kawasan otak yang diaktifkan semasa pemprosesan ganjaran, namun ketersambungan struktur asas yang memotivasi belia untuk jenis ganjaran yang berbeza masih terhad kajiannya. Kajian ini bertujuan untuk memahami mekanisme saraf dalam pelbagai jenis ganjaran dalam populasi belia menggunakan pengimejan resonans magnet kefungsian (fMRI) dan pengimejan tensor difusi (DTI). Tiga puluh satu peserta (17 lelaki, umur min 23±1) telah direkrut. Peserta melakukan tugasan 2-belakang dalam tiga keadaan isyarat (Tunai, IbuBapa dan Sijil) semasa menjalani pengimbasan fMRI dalam mesin MRI 3 Tesla, diikuti dengan pengimbasan DTI. Ketepatan dan masa tindak balas (RT) tugasan 2-belakang telah direkodkan dan peserta dibahagikan ke dalam kumpulan mengikut skor tertinggi mereka dalam tiga keadaan. Analisis kesan rawak (RFX) digunakan untuk mengenal pasti pengaktifan kawasan otak daripada data fMRI. Traktografi kebarangkalian dilakukan pada data DTI. Kawasan permulaan traktografi dipilih adalah daripada bahagian otak untuk ganjaran iaitu putamen dan nukleus akumbens (NAcc), manakala kawasan sasaran ialah korteks singulat anterior (ACC), korteks singulat posterior (PCC), korteks prefrontal dorsolateral (DLPFC), korteks prefrontal ventrolateral (VLPFC), insula anterior dan posterior, dan amigdala. Indeks kebarangkalian sambungan (CPI) dikira daripada setiap kawasan permulaan ke sasaran. Perbandingan

CPI antara kumpulan dianalisis hanya untuk kumpulan IbuBapa dan Tunai menggunakan ujian Mann-Whitney. Korelasi antara CPI dan markah responsif ganjaran (RRS) dianalisis menggunakan ujian korelasi Spearman. Keputusan menunjukkan bahawa 15 peserta mendapat markah tertinggi dalam keadaan Tunai, 16 dalam keadaan IbuBapa dan 2 dalam keadaan Sijil. Pengaktifan otak yang ketara dalam analisis ketiga-tiga keadaan ganjaran didapati di girus occipital tengah sebelah kiri yang terlibat dalam maklum balas ganjaran. Semasa isyarat tunai, terdapat pengaktifan otak yang ketara dalam girus oksipital superior sebelah kiri, yang terkenal dengan peranannya dalam menjangka dan memproses ganjaran kewangan. Isyarat ibubapa mengaktifkan PCC sebelah kiri, yang terlibat dalam perhatian dan dalam melihat wajah yang dikenali dan disayangi secara peribadi, dan putamen sebelah kiri. Kedua-dua isyarat ibubapa dan sijil mengaktifkan girus angular sebelah kiri, yang terlibat dalam menjangka ganjaran. Analisis DTI menunjukkan bahawa kumpulan tunai mempunyai CPI yang lebih tinggi daripada putamen sebelah kanan ke ACC, iaitu kawasan membuat keputusan, berbanding kumpulan IbuBapa. Korelasi negatif didapati antara CPI dan RRS dari putamen sebelah kiri ke insula posterior dalam kumpulan Tunai adalah mungkin disebabkan oleh penglibatan insula posterior dalam pemprosesan kerugian dan hukuman. Korelasi positif didapati antara CPI dan RRS di NAcc sebelah kiri ke PCC dalam kumpulan ibubapa. Kesimpulannya, dapatan kajian ini menunjukkan bahawa ganjaran kewangan untuk diri sendiri mempunyai nilai ganjaran yang lebih tinggi dalam kalangan belia. Tambahan pula, kajian ini mendedahkan peranan penting PCC dalam pemprosesan ganjaran terhadap ibu bapa.

UNDERSTANDING THE BRAIN CONNECTIVITY OF REWARD NETWORK AMONG YOUTHS – A COMBINED FMRI-DTI STUDY

ABSTRACT

Understanding the reward network in youth can shed light on the underlying mechanism that influence important life decisions. Prior studies have pinpointed brain regions activated during reward processing, yet the structural connectivity underlying youth motivation for different rewards is still understudied. This study aims to understand the neural mechanism in different types of reward in the youth population using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). Thirty-one right-handed participants (17 males, mean age 23±1) were recruited. Participants performed 2-back tasks in three cue conditions (Cash, Filial, and Certificate) while undergoing fMRI scanning in a 3 Tesla MRI machine, followed by DTI scanning. The accuracy and response time (RT) of the 2-back tasks were recorded and participants were grouped according to their highest score in the three conditions. Random-effects analysis was used to identify brain activations from the fMRI data. Probabilistic tractography was performed on the DTI data. The seeds were reward areas putamen and nucleus accumbens (NAcc), while targets were anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), anterior and posterior insula, and amygdala. The connection probability index (CPI) was calculated from each seed to target. The CPI comparison between groups was analysed for filial and cash groups only using the Mann-Whitney test. Correlation between CPI and reward responsiveness scores (RRS) was analysed using Spearman's rank correlation coefficient test. Results showed that 15 participants scored highest in Cash condition, 16 in Filial condition and 2 in Certificate condition. Significant brain activation was found in the left middle occipital gyrus, which is involved in reward feedback, in conjunction analysis of the three reward conditions. During cash cue, there was significant brain activation in left superior occipital gyrus, known for its role in anticipating and processing monetary reward. Cue filial activated left PCC, which is involved in attention and in viewing personally familiar and loved faces, and left putamen. Both filial and certificate cues activated left angular gyrus, which is involved in reward anticipation. DTI analysis showed that cash group had higher CPI from right putamen to ACC, a decision-making area, compared to filial group. Negative correlation was found between CPI and RRS from left putamen to posterior insula in cash group, possibly due to involvement of posterior insula in loss and punishment processing. Positive correlation was found between CPI and RRS in left NAcc to PCC in filial group. In conclusion, the findings of this study suggest that monetary reward for self holds higher reward value in youth. Furthermore, this study revealed significant role of PCC in filial reward processing.

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Rewards or punishments motivate human learning and behaviour (Martins et al., 2021). The reward system regulates human emotions such as pleasure and happiness. Reward system involves several cognitive processes, such as decision making and emotional processing (Banich & Floresco, 2019). Nucleus accumbens (NAcc), amygdala, prefrontal cortex (PFC) and anterior cingulate cortex (ACC) have been showed to play an important role for reward processing (Banich & Floresco, 2019; Frank et al., 2019; Lewis et al., 2021).

Understanding how the reward network develops and functions in youth can shed light on the underlying mechanism that influence important life decisions, such as educational pursuits, career choices, and social relationships. According to United Nations Department of Economic and Social Affairs (UNDESA) in 2013, youth is defined as a person within the age range of 15 to 24 years old, which is categorized in the late adolescent stage (Allen, 2024). Adolescence is characterized by well-known accelerated neurobiological changes such as shifts in brain matter composition (Mills & Anandakumar, 2020), increased hormonal release, and neurochemical changes (Berry et al., 2019). Neurochemical modulation of dopaminergic neurons which is essential for engaging in a goal-directed behaviour, decision making, reward processing, and cognitive flexibility changes with age (Berry et al., 2019; Volkow et al., 2017).

Neuroimaging especially functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been widely used as a valuable tool in understanding reward processing. fMRI is one of the protocols in MRI that measures the brain activity by detecting changes associated with blood flow (Glover, 2011). It can be used to assess the brain activation during a cognitive task. Other neuroimaging technique is diffusion tensor imaging (DTI) which is a form of diffusion MRI (dMRI) that uses voxels as a statistical method for data collection (R. Ranzenberger & Snyder, 2021). DTI based tractography provides detailed structural information of the anatomical connectivity (Hagmann et al., 2006). Camara et al. (2009) suggested that the standard fMRI analysis to be supplemented by other method – DTI based tractography, which includes the differential connectivity of the ventral tegmental area (VTA) – ventral striatum system in exploring the reward network.

A previous study by Koch et al. (2010) investigated the individual ability to reduce processing resources with decreasing uncertainty in direct relation to individual characteristics in white matter (WM) brain structure. The fMRI revealed that more successful learners exhibited stronger activation decreases with decreasing uncertainty (Koch et al., 2010). The DTI analysis showed an increased mean and axial diffusivity in, among others, the inferior and superior longitudinal fasciculus, the posterior part of the cingulum bundle, and the corpus callosum were detectable in less successful learners compared with more successful learners (Koch et al., 2010). Most importantly, there was a negative correlation between uncertainty-related activation and diffusivity in a fronto-parieto-striatal network in less successful learners only, indicating a direct relation between diffusivity and the ability to reduce processing resources with decreasing uncertainty (Koch et al., 2010). These findings indicate that interindividual variations in white matter characteristics within the normal population might be linked to neuronal activation and critically influence individual learning performance (Koch et al., 2010).

Therefore, in this study, fMRI and DTI were used to understand the neural mechanism in different types of reward. The goal of this study is to determine the brain activation and structural connection probability index in three different types of reward, i.e., cash, filial and certificate.

1.2 Problem Statement and Study Rationale

Rapid advances in science and technology, as well as increasing social complexities, also underpin the importance of morals, values, and ethics and their benefits to society (Chowdhury, 2016). Technological advancement has create communication barriers between youth and their parents on a daily basis which leads to a decrease in parental respect (Eva N., 2016).

Different parts of the brain are activated when processing different types of reward. Most of the previous research studied the different responses of the brain connectivity to non-monetary and monetary reward, in which the non-monetary reward was not specified as filial or certificate. Instead, the non-monetary reward was studied mainly in relation to addiction or obesity (Reyes et al., 2020), and humorous reward (Chan et al., 2018). A certificate is categorized as a social reward since it is related to acknowledgement and is considered non-monetary reward. Particularly, articles related to filial in neuroimaging specifically fMRI or DTI is infrequent. However, there is a study by Guerra et al. (2011) that investigated filial and romantic love using electroencephalogram (EEG) and found that both stimulates an intense positive emotional reaction but the magnitude of some peripheral and subjective indices of emotionality, such as zygomatic activity, valence, arousal, and dominance, were different. Despite potential differences in how cash, filial, and certificate rewards are processed, there's limited neuroimaging research specifically on the structural and functional connectivity of the youth reward network in response to these reward categories.

Therefore, in this study, we will compare the neural mechanism in all three different rewards: cash, filial and certificate among youths using fMRI and DTI. This research aims to study how youths choose between different types of rewards and how the rewards affect their task performance. This study will provide a baseline for comparison with youths who may have different reward processing patterns due to various psychological or neurological conditions. Plus, youths are the ones who will be entering into the workforce and hold the key positions in the country, the future decision-makers, and leaders.

1.3 Research Questions

1. Are there any differences in the accuracy of the 2-back task between reward categories (cash, filial, and certificate) among youths?
2. Are there any differences in brain activation between the three types of cues and the 2-back task (cash, filial, and certificate) among youths?
3. Are there any differences in the structural connectivity of reward networks among the three different types of rewards in youths?

1.4 Research Hypotheses

1. There is no significant difference in the accuracy of the 2-back task between reward categories (cash, filial, and certificate) among youths.
2. There is no significant difference in the patterns for brain activation between three types of cues and the 2-back task (cash, filial, and certificate) among youths.

3. There is no significant difference in the structural connectivity of reward networks in the three different types of rewards in youths.

1.5 Research Objectives

1.5.1 General Objectives

To investigate the neural mechanisms between three types of reward category (cash, filial, and certificate) in youths using fMRI and DTI.

1.5.2 Specific Objectives

1. To compare the accuracy of the 2-back task between reward categories (cash, filial, and certificate) among youths.
2. To determine the patterns for brain activation pattern between three types of cues (cash, filial, and certificate) among youths.
3. To determine the structural connectivity of reward networks in three different types of rewards in youths.

1.6 Benefits of the study

This study has the potential to significantly advance our understanding of how cash, filial, and certificate rewards shape the developing youth brain. More specifically, it will elucidate differences in how these rewards impact brain activation and structural connectivity within the reward network. Plus, the findings of this study can help people to make informed motivational strategies, for instance, it could help parents, educators, and youth professionals to tailor their approaches to better motivate and engage young people. The results from this study will add to the broader body of knowledge about reward processing, with potential applications for understanding decision-making, behaviour modification, and even the treatment of certain mental health conditions.

CHAPTER 2

LITERATURE REVIEW

2.1 Reward System

Reward processing involves reward anticipation and reward evaluation (Camara et al., 2009; Chan et al., 2018; Oldham et al., 2018). Chan et al. mentioned that phases of reward anticipation and reward outcome involved motivational, learning, and affective components (Chan et al., 2018). Reward anticipation is characterised by ‘wanting’, the experience of incentive salience that triggers a motivational impulse to obtain a reward, while reward outcome is characterised by ‘liking’, the hedonic enjoyment experienced upon consuming the reward (Chan et al., 2018).

Oldham et al. (2018) further investigated the anticipation and outcome phases of reward and loss processing. These investigators found that striatum and thalamus were both activated in reward and loss processing. This is because ventral striatum is associated with motivational process, independent of stimulus valence (Oldham et al., 2018). Striatum was activated during both reward anticipation and outcome, whereas orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC) was activated only during reward outcome. Aligned with the study by Chan et al., reward anticipation involves the fronto-subcortical-limbic network, which includes the ventral striatum, the PFC and insular cortex (Chan et al., 2018; Oldham et al., 2018). In addition, ventral striatal activity during both reward and loss anticipation was restricted to the dorsolateral NAcc, which has a key role in motivational processes (Oldham et al., 2018).

Plus, the putamen is closely associated with dopamine, the main neurotransmitter in reward system. The volume of the putamen has been linked to various neuropsychiatric conditions, affecting emotional processing, attention, and reward-seeking behaviours (Huskey et al., 2018; Ren et al., 2023; Shen et al., 2020).

The putamen is crucial for processing rewards in a more action-oriented and stimulus-specific way compared to other reward-related brain regions like the caudate and NAcc (Gujar et al., 2011).

Reward processing might be altered in individual with certain medical conditions, e.g., obesity. Addiction and obesity have strong parallels with each other (Camara et al., 2009), where the previous study has shown reduced or similar sensitivity to incentives in obese adults compared to lean subjects (J et al., 2017; Kube et al., 2018). Previous studies suggest that the network connectivity is different between obese patients and normal-weight patients. In obese participants, a greater activation of the reward system to food stimuli was observed (Camara et al., 2009). Reward and loss strongly drive human behaviour, and their connection with cognitive control is crucial for goal-directed conduct. Optimal white matter integrity is important for an efficient interaction among reward-related brain regions.

2.1.1 Reward Mechanism

The main neurotransmitter in reward system is dopamine (Camara et al., 2009; Gibson, 2017). Neurons releases dopamine, which subsequently binds to the dopamine receptors on other neurons. The dopamine reward system creates feelings of desire and operant conditioning, specifically positive reinforcement (Gibson, 2017). Referring to Figure 2.1, dopaminergic neurons originated from the midbrain part, specifically the VTA and substantia nigra (SN). In the mesolimbic pathway, dopamine is projected to the ventral striatum, which contains NAcc that controls the body’s motor functions (Camara et al., 2009). The NAcc plays a vital role in the monetary reward anticipation, where dopamine release in the NAcc during reward consumption is lower than during reward anticipation (Chan et al., 2018). The neurotransmitters also travel through the hippocampus and amygdala, which are responsible for memories and emotions, respectively. Another dopamine pathway that is associated with the reward system is mesocortical pathway where the dopamine also originated from VTA travels to the OFC, ACC, and PFC, which is in charge of attention and planning.

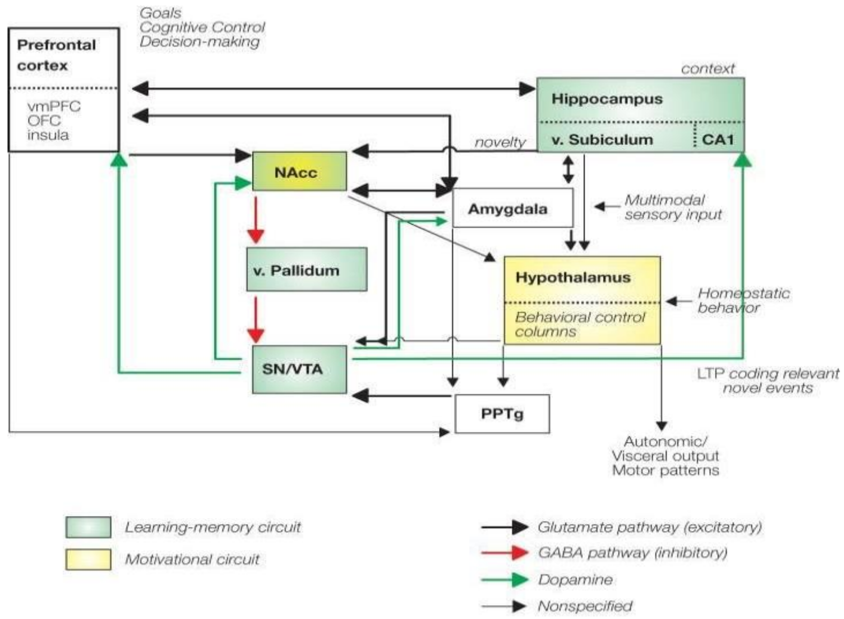

Figure 2.1 Reward pathways adapted from Camara et al. (2009).

VTA and NAcc are also important in learning and motivation, other than for immediate processing of rewards (Camara et al., 2009; Oldham et al., 2018). Learning involves the hippocampal-VTA (HP-VTA) loop, where the hippocampal signals might be sent to the midbrain (SN/VTA) through NAcc and ventral pallidum (VP), which is an essential region for 'liking' sensation (Camara et al., 2009). The activation of SN/VTA and the hippocampus has also been associated with novelty processing and facilitation of memory formation (Camara et al., 2009). The structures of the limbic system that are related to motivation are mainly NAcc and amygdala. The pathway of motivated behaviour involves the prefrontal cortex, the VTA, the amygdala, NAcc and the VP (Rajmohan & Mohandas, 2007).

2.2 Youth and reward

Studies have examined responses to reward in youths. Liu et al (2022) examined neural activation during reward expectancy and attainment and found that reward expectancy activated regions within the fronto-striatal reward network, thalamus, occipital lobe, superior parietal lobule, temporoparietal junction, and cerebellum. Previous studies have also shown associations between parenting behaviour and their offspring brain responses in neural networks involved in emotion regulation and reward processing (Chaplin et al., 2022). It was found that low parental warmth was associated with higher response to potential rewards in reward processing networks in the medial prefrontal cortex (mPFC), striatum, and amygdala (Casement et al., 2014).

On top of that, there are also differences in how adult and youth processed the rewards. For example, lower fractional anisotropy (FA) in uncinate fasciculus (UF) indicates higher antisocial behaviour (AB) in adult, whereas youth with AB shows higher FA in UF. This is because, AB in adult is more related to psychopathy, whereas AB in youth is likely related to more behavioural problems (Waller et al., 2017).

2.3 Neuroimaging and Reward

2.3.1 Combined fMRI – DTI Studies

Since the early ‘90s, fMRI and DTI have evolved and been constantly used for their own speciality to study the white matter (WM) microstructures and grey matter (GM) functions for their effectiveness, non-invasiveness and convenience (Zhu et al., 2014). fMRI guided fibre tracking is one of the fusions between fMRI and DTI. During fMRI guided fibre tracking, the subjects undergo a specific task-based fMRI. The activated regions that have the most prominent responses to the task are identified as region of interest (ROI) (Zhu et al., 2014). The ROIs identified during the task-based fMRI act as seed points for DTI tractography, in which the probabilistic fibre tracking algorithm is commonly used (Zhu et al., 2014). Besides task-based fMRI, resting-state fMRI (rsfMRI) also plays a crucial role in fibre selection. The regions of resting-state, including default mode network (DMN), can be identified as ROIs to help filter the whole-brain fibre tracts (Zhu et al., 2014).

The justification of fMRI guided fibre tracking or filtering is that by using ROI from task-based fMRI, the number of fibre tracts to be measured can effectively be reduced, which makes the DTI tracking more efficient and focused. Plus, this method enables selective isolation and study of the distinct functionally related fibre bundles (Zhu et al., 2014). This is because the task-based fMRI has been widely used as a standard approach to localising and mapping functionally specialised brain regions under specific task stimulus (Zhang et al., 2016; Zhu et al., 2014). Lastly, fMRI is generally considered more reliable than cortical folding based anatomical landmarks to target the group-wise corresponding ROIs in a group analysis (Zhu et al., 2014).

An example of a recent study using combined fMRI and DTI is a study by Alotaibi et al. (2023). This study investigated neural changes over three days of learning Arabic phonetic categorization as a new language. It was observed that training-related hemodynamic fMRI signal and FA value increased in the left inferior frontal gyrus and positively correlated with behavioural improvement (Alotaibi et al., 2023).

2.3.2 fMRI

2.3.2(a) fMRI mechanism

Blood-oxygen-level-dependent (BOLD) is characterized by hemodynamic response function (HRF) which describes the effects of transient changes in blood flow, volume, and/or oxygenation which makes it possible to measure the brain activity (Rangaprakash et al., 2021). When there is an increase in local neuronal activity, it stimulates higher energy consumption in the brain region, thus increasing the blood flow to the region (Hillman, 2014) (refer Figure 2.2). This will subsequently increase oxy-/deoxy-hemoglobin ratio in the brain region.

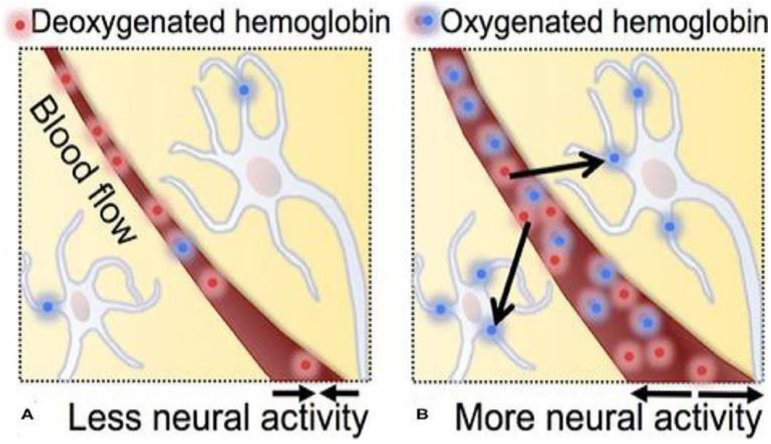

Figure 2.2 BOLD responses adapted from Amanamba et al. in 2020.

2.3.2(b) Brain activations of reward

Oldham et al. stated that heterogeneous task stimuli (e.g. monetary, humorous or food), may occupy distinct cognitive processes and reward related networks (Bartra et al., 2013; Clithero & Rangel, 2013; Liu et al., 2011a). For instance, monetary rewards engage less activity in the amygdala/insula and uniquely engage the anterior OFC compared to food and erotica (Sescousse et al., 2013).

Previously, Chan et al. (2018) studied the mesolimbic reward system and its distinct processing function between monetary and humorous rewards using fMRI (Chan et al., 2018). In the study, reward processing was divided into two phases which were reward anticipation and reward outcome. As for the type of rewards, there were monetary and humorous rewards. Monetary rewards elicit pleasure, whereas humorous rewards elicit feelings of amusement during the hedonic consumption phase. In addition, this study uses psychophysiological interaction analysis (PPI) to examine the functional activity of the NAcc and amygdala during reward-related activation. The study found out that the amygdala-midbrain circuit is responsible for humorous gains during the outcome phase, whereas the NAcc-ACC circuit is responsible for monetary rewards in the anticipation and outcome phase (Chan et al., 2018).

A study by Vila et al. (2019) included the faces and names of the father, mother, partner and subject's best same-sex friend as stimuli to compare the emotional mechanisms activated by loved faces and names. Using fMRI, a set of overlapping areas that includes the anterior cingulate and inferior frontal areas were activated in response to loved familiar faces and names displays. These areas have been implicated in a variety of cognitive and emotional processes, including empathy and subjective happiness (Vila et al., 2019). Previous fMRI studies on reward processing have detected differences in activated signals between reward anticipation and reward reception in humans (Liu et al., 2011b).

2.3.3 DTI

2.3.3(a) DTI mechanism

When a voxel contains scalar values comprising a vector, it is called a tensor, which is where the name DTI originated from (R. Ranzenberger & Snyder, 2021). DTI uses Brownian motion, molecular water diffusion in a three-dimensional space that moves in an isotropic state to produce an image (Hagmann et al., 2006; R. Ranzenberger & Snyder, 2021). Anisotropy is a term commonly used in DTI, which means the opposite of isotropy (Figure 2.3, adapted from (https://www.radiologycafe.com/frcr-physics-notes/mr-imaging/diffusion-weighted-imaging/)). When the diffusion of water has a directionality, and the movement of water is no longer random, it is called anisotropy (R. Ranzenberger & Snyder, 2021).

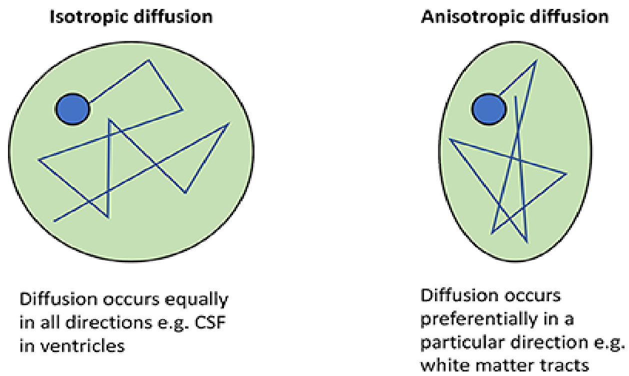

Figure 2.3 Isotropic vs anisotropic diffusion.

The greater the anisotropy means the diffusion of water molecules is more directional and linear (R. Ranzenberger & Snyder, 2021). DTI provide an indirect method of assessing the neuroanatomy structure on a microscopic level using water molecules' degree of anisotropy and the structural orientation within a voxel (R. Ranzenberger & Snyder, 2021). Therefore, DTI is considered as a virtual dissection of white matter tracts in vivo (Chen et al., 2016), where the orientation, location, and anisotropy of the tracts can be measured and evaluated (R. Ranzenberger & Snyder, 2021).

2.3.3(b) Structural connectivity of reward

Previously, Koch et al. (2014) used a combined fMRI-DTI study to correlate NAcc BOLD signal upon receiving monetary reward in different white matter characteristics. The study found that higher WM integrity, as measured by FA in the cingulate and corpus callosum, the inferior fronto-occipital fasciculus, the anterior thalamic radiation, and the anterior limb of the internal capsule, was positively associated with increased reward-related activation in the NAcc (Koch et al., 2014). Another study investigated the incentive sensitivity and its relationship of WM integrity in normal weight and overweight groups using tract-based spatial statistics (TBSS). It was revealed that there is a positive relationship between FA and loss avoidance accuracy in the normal weight group (Reyes et al., 2020). Previous study explored the relationship between WM properties and reward-based behaviour in healthy participants and found that WM properties in the corpus callosum, right uncinate fasciculus, left ventral cingulum, and accumbofrontal tracts were inversely associated to reward-triggered performance benefits (indexed by faster reaction times) (Park et al., 2021).

2.4 Summary

Based on the previous studies, it was revealed that different types of reward involved different brain activations. To ensure the homogeneity of the population, youth was selected since many previous studies investigated the reward network, mostly addiction in youths. Plus, youth is an important time in human life that involves decision-making and learning process. Many of the previous studies investigated the reward network using monetary reward and social reward, but only a few made comparison between the types of reward. Moreover, no known previous study has investigated on filial reward and brain activation, similarly with reward in the form of certificate.

2.5 Conceptual Framework

Figure 2.4 shows the conceptual framework of this study. This study investigates how the different factors around youth and the types of reward cues affect task performance. This study also determines the structural connectivity in different types of rewards based on brain activation.

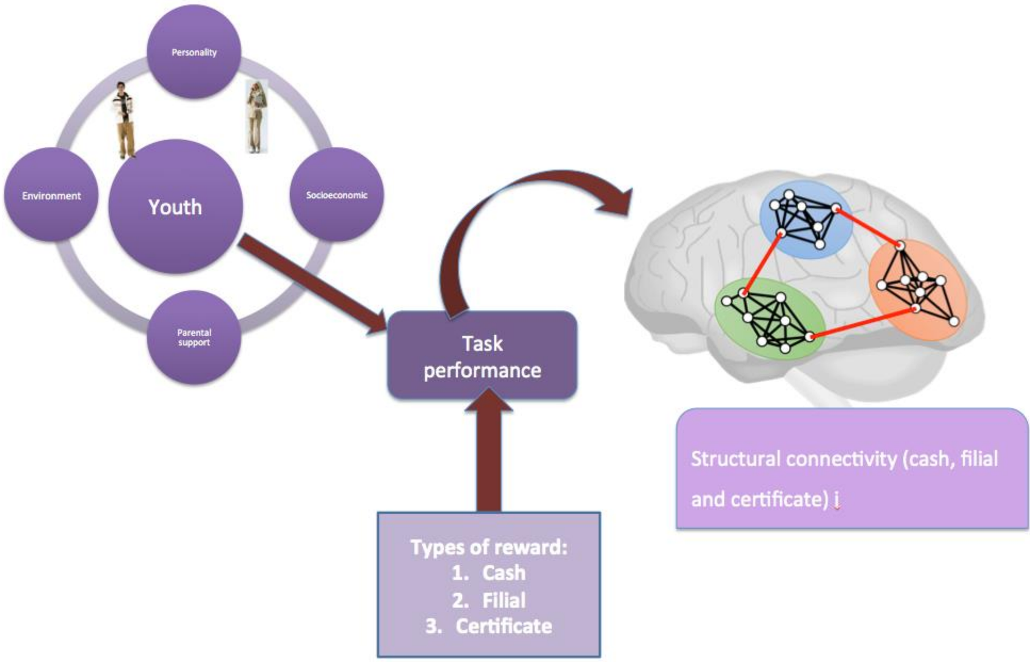

Figure 2.4 Conceptual framework of this study.

CHAPTER 3

METHODOLOGY

3.1 Participants

Thirty-one participants (17 males and 14 females) were recruited among under- and post-graduate students from Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan using purposive sampling through advertisements placed on public notice boards, word-of-mouth and mailing lists. They should be students with ages ranging from 18 to 24 years old during the data collection. This is to ensure the common interest of the participants. This study is a cross-sectional experimental study design. Participants performed a block-design 2-back task under three reward cue conditions (Cash, Filial, Certificate). They were rewarded according to the accuracy, which is the highest score obtained among the three conditions. Participants underwent a preliminary screening for exclusion and inclusion criteria which was done through online questionnaires to increase the efficiency of the experiment. Only participants who passed the preliminary screening were invited to participate in the study. Written informed consent was obtained before the start of the study. Participants were remunerated RM70 for participation inside the scanner, plus a separate reward in the form of either cash to self, cash to parent, or certificate depending on their scores. The data was collected and analysed at the Health Campus of Universiti Sains Malaysia in Kota Bharu, Kelantan. This study was approved by the Human Ethics Committee Universiti Sains Malaysia (USM/JEPeM/21100659).

3.2 Sample Size Estimation

The sample size needed for robust imaging analysis that provides information relevant to extrapolation to the general population-based upon rigorous analysis methodology is n=12 (Szucs & Ioannidis, 2020) Using G-power (3.1, Heinrich-Heine-University) sample size calculator, the total sample size calculated was 28. The input parameters were number of groups = 1, which is youth, number of measurements = 3, which are three different types of reward, the power of the study is 80% and the effect size is 0.25. The actual scanning experiments would need 28 volunteers, including dropout rate of 10%. Therefore, in total, the study would need about 31 healthy participants (refer Figure 3.1).

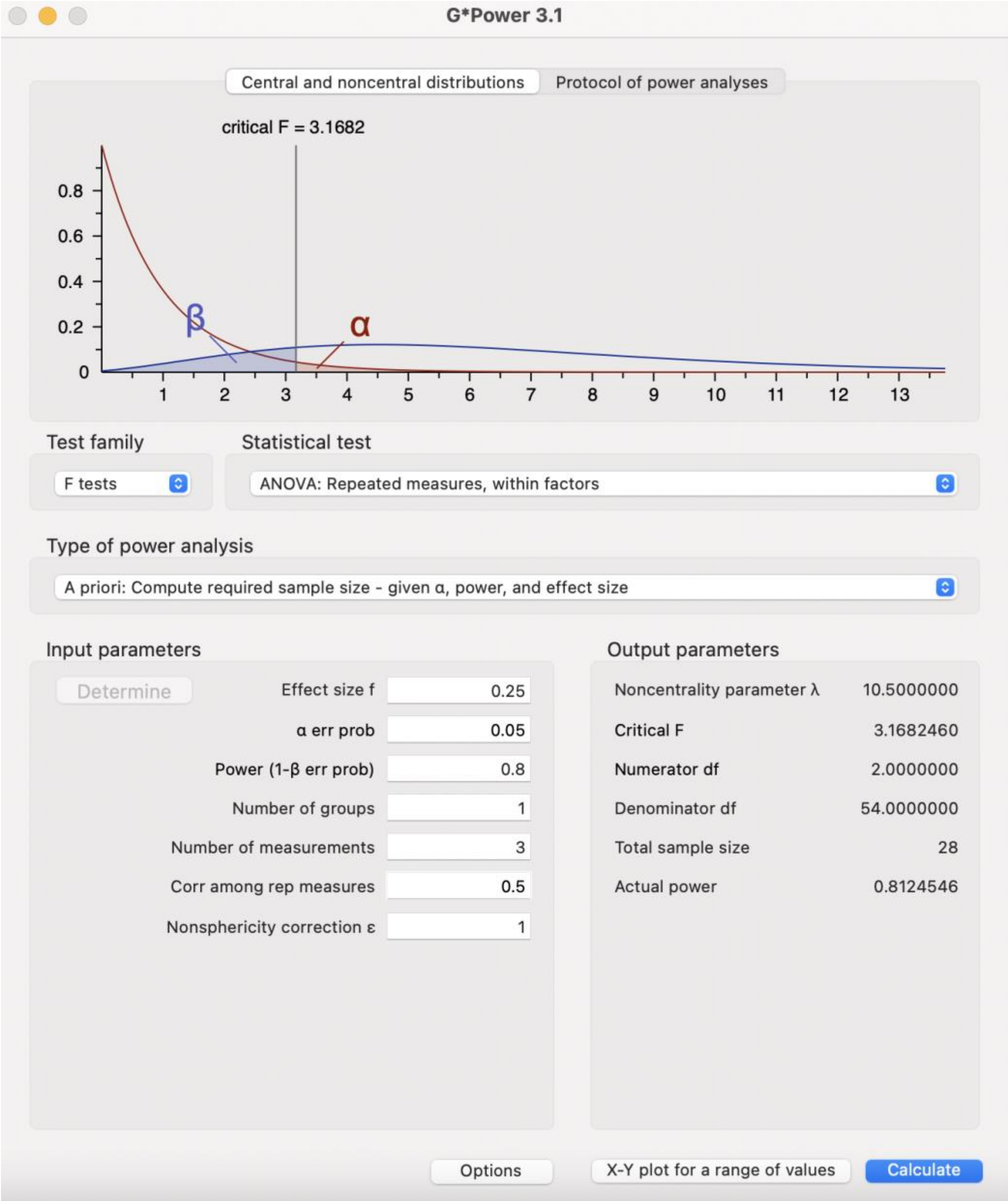

Figure 3.1 Sample size calculation using G-power 3.1.

3.3 Inclusion and Exclusion Criteria

Participants must be healthy undergraduate or postgraduate students from Health Campus USM, right-handed (according to Edinburgh Handedness Inventory Questionnaire) and young adults within the age range of 18 to 24 years old(United Nations Department of Economic and Social Affairs (UNDESA)., 2013). Participants must be able to understand instructions in the MRI scanner, and able to provide written informed consent. The exclusion criteria for this study are any history of medical disorder that may affect the brain function (e.g., Parkinson's disease), history of psychiatric disorder requiring current psychotropic medication (e.g., Lorazepam) or previous inpatient psychiatric hospitalisation, taking drugs that may influence the central nervous system, i.e., antidepressants, antiepileptic medication and sleeping pills, and substance abuse. Participants must not be pregnant, claustrophobic, and have any presence of contraindications to MRI scanning, i.e., metallic implants, stents, and clips, which was confirmed by verbal questioning, and double confirmed by checklist questionnaires and consent before entering the MRI scanner.

3.4 Research Tools

Several research tools were used for the data collection and analysis in this study which includes 3-Tesla Philips Achieva MRI (Philips Acieva, Philips, Best, The Netherlands) scanner which was used for the data collection. As for fMRI ROI analysis, MATLAB R2022b (www.mathworks.com) and Statistical Parametric Mapping 12 (SPM12) were used. Probabilistic tractography technique via FMRIB Software Library version 6.0, specifically the FMRIB Diffusion Toolbox (FDT) were used for structural connectivity (DTI) analysis.

3.5 Study Flowchart

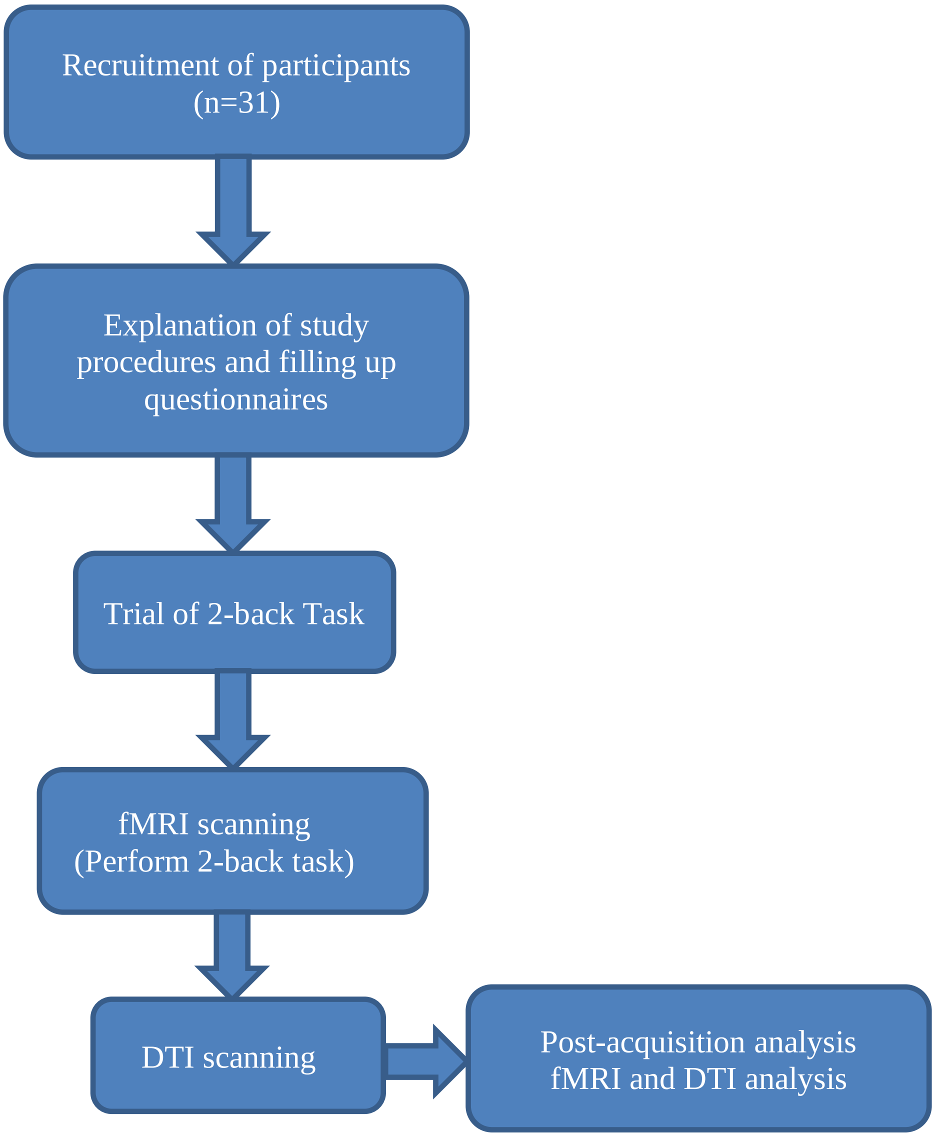

Figure 3.2 Flow chart of the study.

3.6 Study Procedure

The participants underwent MRI scanning for this experiment. Before the scanning, the participants were given instructions related to cues and a cognitive task. The participants were briefed regarding the task inside the fMRI and how there will be a presentation of cues for three reward conditions. The three reward conditions were:

1) Cash: the participant will be rewarded with cash money of RM70 separately from the honorarium.
2) Filial: parents will be sent a gift, i.e., cash of RM70 and letter informing them of their child's participation in the study.
3) Certificate: participants will be awarded a certificate of participation in a brain study.

Following each cue, participants performed the 2-back task, where the scores from each cue would determine the reward they would obtain. A trial of 2-back task was given to the participants in the simulator room to ensure they fully understood the task. The participants were told that they would get the reward for real according to their highest score for 2-back task in any cue except the score for neutral cue which would not be counted. The cues for the reward form were presented prior to each run. A brown circle was presented for the neutral cue, money illustration for the cash cue, cartoon illustration of parents for the filial cue and an illustration of a certificate for the certificate cue.

Participants underwent four runs of 2-back task during fMRI scanning sessions, followed by DTI measurement. For fMRI scan, each run contains two blocks of 2-back task with 2 different cues, whereby in total, participants performed two blocks of 2-back task for each cue (two for neutral cue, two for cash cue, two for filial cue, and two for certificate cue) (refer Figure 3.3). The order of the cues was pseudorandomised among the participants. Figure 3.3 shows the example of block design for reward paradigm. used in this study.

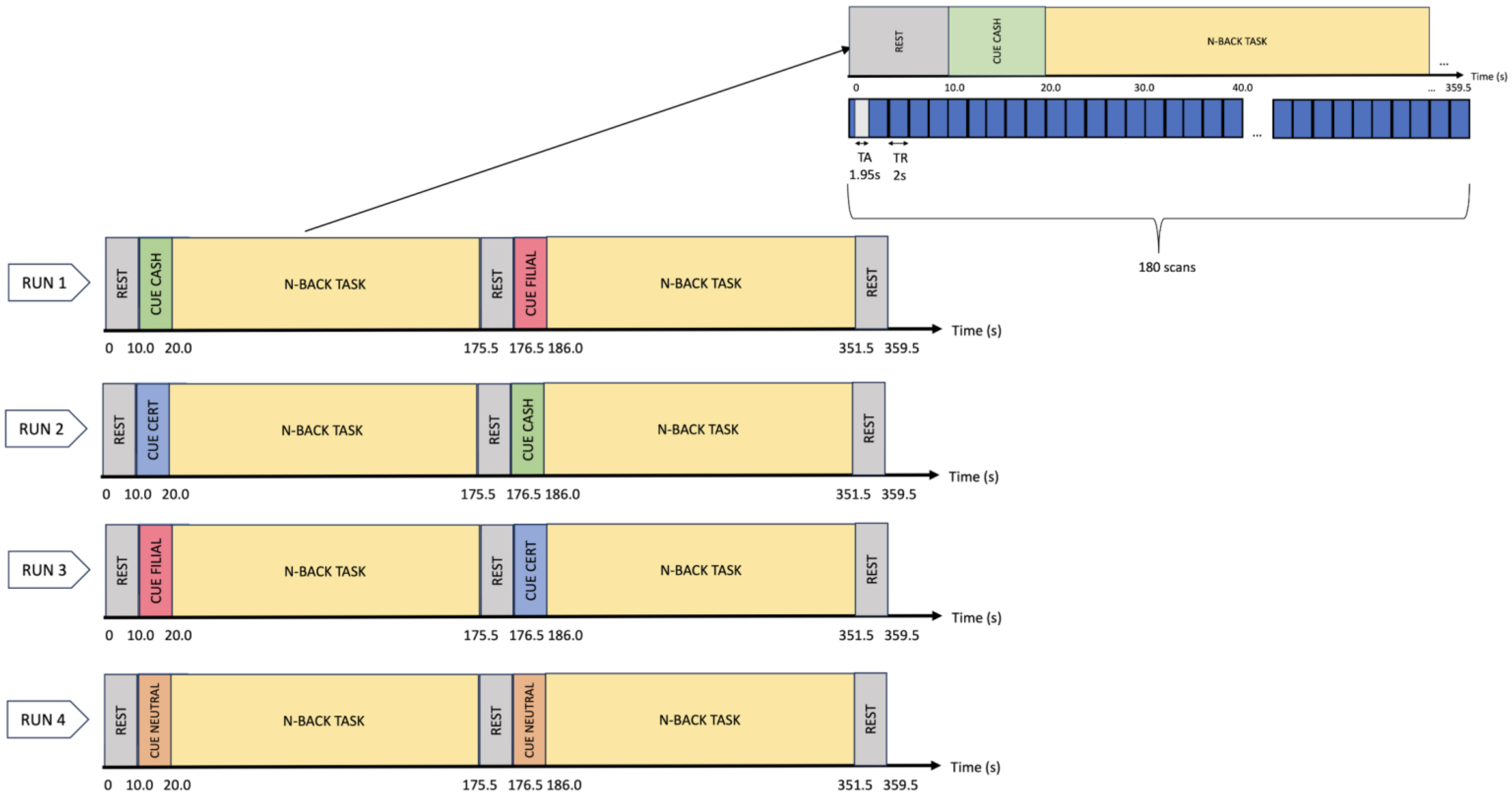

Figure 3.3 Example of block design of reward paradigm used in this study. There are four runs of 2-back task, each run containing two blocks of 2-back task with 2 different cues (TA = acquisition time, TR = repetition time).

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3.6.1 Experimental procedure

During the scanning, the participants were immobilized with straps around their body to ensure no movement, and a head strap was also placed around their head. Non-conducting pads were placed in between the thighs to ensure no skin-to-skin contact during the scan to prevent from skin burning. Then, the cues and 2-back task were presented on a screen at the foot of the scanner bed by a projection monitor and viewed using a head coil mirror. Referring to Figure 3.4, a series of shapes in white color were displayed on a black background for 0.5 seconds each, with 1.5 seconds intertrial interval where a fixation cross was shown at the centre of the screen. There was a 10 second rest at the start of each run (before cue) and at the end of each run (after the last stimuli). Participants were instructed to answer the task by pressing a button if either of the two previous shapes were shown on the screen. There would be no score recorded if the button was not pressed. The 2-back task lasted 5 minutes and 55 seconds for each run, with a total of 156 trials, including 114 non-target stimuli and 42 target stimuli for each run. Non-target stimuli were distractor stimuli where participants needed to withhold their response, while target stimuli were the correct stimuli that require participants to respond, indicating that the stimulus matches the one presented in the two previous trials (2-back task).

At the end of the experiment, the scores were added up and they were rewarded accordingly, i.e., besides the honorarium, the participants who scored highest in cash condition were given RM70 for themselves. In contrast, participants who scored highest in the filial condition were given RM70 to their parents, along with a letter declaring their participation in this study. Participants who scored highest in certificate condition were given a certificate with the signature of the Faculty’s Dean, in addition to the honorarium for their participation.