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Predicting the Brain Distribution of Consequence by Mathematical Means

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Contents

ABSTRACT

Functional Magnetic resonance Imaging (fMRI) is a non invasive tool used to examine the cognitive and affective processes in the brain. It is important to note that, although fMRI is indirect, it has been used with success to corroborate the results from the animal into the human brain and improve models to include more common human characteristics that influence behavior. This work aims to answer to the question "Which cortical and subcortical areas are involved in anticipation of the consequence?" by doing a Activation Likelihood Estimation Meta-Analysis over reported results of several papers from literature. These reports used fMRI to track the brain hemodynamic response of the subjects in different tasks and reported the peak coordinates of activation. The prefrontal cortex was observed to contain a consequence network that was modulated by being rewarded with a high incentive in a decision-making task. Another concordant regional activation in the frontal lobe, insula and putamen was found during "n-back" task for working memory and decision-making tasks.

Keywords: consequence; fMRI; ALE meta-analysis; prefrontal cortex; reward value; working memory.

Chapter 1

Introduction

In order to adapt successfully to the environment, animals must anticipate rewards and penalties, recognize their nature and respond to the stimuli appropriately by changing their attention or arousal level. Several Imaging studies have shown that human brain activity is associated with cognition of abstract rewards and penalties. Gambling tasks [Aki+03; Cox05; Chr+09; Del+00] are an used laboratory model for investigating the response of the human brain to this type of stimuli. The brain structures like bilateral anterior cingulate, medial prefrontal cortices and dorsolateral prefrontal cortex (DLPFC) [Aki+03] involved in rewards and punishments have been identified in studies of humans. The lateral orbitofrontal cortex(OFC) was found correlated [ODo+01] with the activation when subject to punishments and deactivation following rewards on the reverse of what was discovered in the Striatum regions [Del+00]. Moreover, the OFC activation magnitude is proportional to that of the reward/penalty received. Cox et al. [Cox05] correlate this region with both context-dependent events based on acquired reward value and rewarding stimuli. The rewarding effect showed, at the brain level, that the DLPFC activation is correlated with the reward quality, quantity and the motivational context. In their work MacDonald et al. [Mac+00] dissociated the role of DLPFC and Anterior Cingulate Cortex (ACC) using functional magnetic resonance imaging (fMRI) and a version of Stroop task for ink color recognition. They related DLPFC with a role in the implementation of cognitive control and ACC with a role in performance monitoring. In a recent study, [Ros+16] it was found that the opposite effects of increasing reward magnitude affect the activation of the left DLPFC and dorsal caudate.

The brain must encode both information about motivational relevance and the affective valence of expected outcomes in order to represent value for learning and decision making [Car09]. Decision-making is a complex, non-unitary process that integrates cognitive and emotional processing of action consequences that determine ongoing behavior. Using a variation of one of the most influential decision-making paradigms, the Iowa gambling task [Chr+09], it was shown that areas in PFC are sensitive to accumulating negative outcomes and that they drive adaptive choice in the task like shifting away from disadvantageous options. In contrast, it was shown that in working memory cognitive experiments [Nob+04; Rei+13] the prefrontal activation could not have been related to decision making or response selection.

Using a fMRI study that examined the neural activation in relation to working memory load using the n-back task, Beneventi et al. [BEN+07] found that the prefrontal regions of the brain's hemodynamic response to facial expression may represent the integration of both working memory and emotional processing. Activation in the same brain area was found by Seo et al. [Seo+12] in his 1-back and 2-back task using letter stimulus and by Pochon et al. [Poc+02] for a more demanding 3-back condition.

1.1 Goal and motivation

An essential feature of adaptive behavior is the ability of humans and animals to detect the effect of their actions on environmental events, allowing them to regulate the acquisition and execution of new and existing behavioral strategies based on consequence. Considering that responding requires effort, humans derive benefit from encoding the likelihood of receiving a valued result and increasing performance when there is a high likelihood or vice-versa when there is a low likelihood. The present work set out to address the following question:

"Which cortical and subcortical areas are involved in anticipation of the consequence?"

Specifically, the current work aims to investigate the neural substrate of contingency detection in humans, and thus to provide an atlas, in stereotaxic space, of brain areas related to working memory with "n-back" task, decision making and reward value and their conjunction.

Blood oxygen level-dependent (BOLD) functional magnetic resonance imaging(fMRI) is an ideal tool to measure indirectly the neural activity [WSD16] by tracking small changes in blood flow and is used to examine the brain's functional anatomy. This method led to the appearance of numerous papers over the last two decades in reward processing which reported the center coordinates of the brain activation regions. Correlated with the corrected algorithm for ALE meta analysis which made it possible to give an approximation of the likelihood that a given coordinate can be truly activated during an experiment, made us believe that this type of study can be conducted with success. By modeling reported brain coordinates quantitatively and comparing their overlap across studies in standard brain space, meta-analyses of this type facilitate the combination of data from diverse neuroimaging experiments.

1.2 State of the art

In order to perform a comprehensive analysis of various papers from the literature that measure the hemodynamic response of the brain in conjunction with neuroimaging data and report the peak activation centers, different meta-analysis methods can be applied. Activation Likelihood Estimation (ALE) meta-analysis [Eic+09; Eic+12; Eic+16; Tur+02; Tur+11], multi-level kernel density analysis (MKDA)[WLK07; Wag+09] and signed difference map analysis (SDM) [Pal+12] were used with success by researchers in order to pinpoint brain regions that are consistently activated when performing a particular type of task [RCM21; YA18; Owe+05; Keu+14; Die+12].

The ALE Meta-Analysis was introduced in 2002 concomitantly by Turkeltaub et al. [Tur+02] and Chein et al. [Che+02]. While Turkeltaub et al. presented a meta-analysis of the single word reading which was verified with their own fMRI study using thirty-two subjects on the same task, Chein et al. concentrated on a meta-analysis of working memory studies with which they verified their findings in two sub-regions of the left inferior frontal cortex. Becoming part of the BRAINMAP software suite and available to use openly under the name GingerALE [Bra22], this method became one of the most used for coordinate-based meta-analyses. The key idea of the ALE algorithm is to consider the activation foci as a center of probability distribution and not in a discrete way. Thus, a Gaussian spatial variance model is used in conjunction with the reported peaks as the best point estimator to accommodate the spatial uncertainty associated with the neuroimaging findings [Eic+09]. In the end, a voxel-by-voxel ALE map is obtained by combining the activation probabilities just obtained of each experiment or group of subjects [Tur+11]. Furthermore, the null hypothesis of random spatial association between experiments is used to distinguish the true convergence of foci from the random clustering end to eliminate the noise.

Until now there were developed three different approaches in order to tackle the multiple comparisons in the whole brain:

1. a cluster-level inference in order to address the family-wise error rate correction that involves thresholding the statistical image of the uncorrected voxel-wise p-value. A set of random experiments with the same characteristics present in real data are simulated. Clusters that are not covered enough time (threshold) by the clusters given from the generated data are discarded. This correction method was proved to be the most appropriate to use for statistical inference [Eic+16];

2. a voxel-level family-wise error correction procedure that controls the likelihood of observing a given z-value if foci were distributed randomly [Eic+12];

3. a procedure that controls the false discovery rate (FDR) introduced by Laird et al. [Lai+05].

The kernel density analysis (KDA) is very similar to the ALE, both focused on the peak coordinates, but in this case, the smoothing kernel is spherical with radius r. These kernels were tested and was demonstrated that the best value for r is somewhere between 10 and 15 mm [WJR04]. In the end, KDA uses Monte Carlo simulation to obtain a threshold and establish statistical significance against a null hypothesis. A number of permutations are computed, typically 10000, where a set of n peak coordinates are generated and randomly distributed across the brain. The value of maximum density is kept at each permutation and is created a maximum density distribution under the null hypothesis so that the voxels whose density is greater than 95% of the Monte Carlo maps are kept.

The MKDA method was introduced as an approach to the KDA method limitation that there are no inter-study differences, meaning that a study can influence decisively the meta-analysis if it reports a high number of peaks in a close range. The novelty of the MKDA method consists of the introduction of contrast maps (CMs) [KW10] which take into account the multilevel nature of the data. Also, the authors introduced various study weighting methods based on the study sample size and whether or not the study used

fixed-effect analysis. This shortage was tackled by Turkeltaub et al. [Tur+11] for ALE, in a similar manner, by taking into consideration the within-experiment and within-group effects.

The Signed Differential Mapping now called Seed-based d Mapping (SDM)[Rad+22] was introduced by Radua et al. [RM09]. This method consists in creating statistical maps for each experiment based on peak coordinates using an unnormalized Gaussian kernel. Meta-analytic maps can be obtained voxelwise by calculating the mean from the previously created maps, weighted by the inverse of the sum of its variance plus between-study variance [Rad+11]. A particularity of the SDM method is the fact that it can include positive and negative effects in the same map which means that some regions can be canceled when both effects are present. Later, anisotropic kernels were added to improve the method [Rad+14].

Even though SDM and ALE focus on determining the overlap between the location probabilities reflecting the uncertainty associated with the peaks, whereas MKDA focuses on how many foci are reported within a particular voxel, all three methods are vastly used by researchers for coordinate-based meta-analysis.

Chapter 2

Analysis

2.1 Data

A comprehensive search for eligible fMRI articles was performed using the PubMed database (https://pubmed.ncbi.nlm.nih.gov/). The key terms used in order to find the relevant articles were "working memory", "reward magnitude", "reward value", and "decision making". All of these were combined with the term "fMRI" since this thesis is based on data obtained by this non-invasive method. Based on the information found in this papers, on the fact that the experiments made involved healthy subjects and had the activation foci reported as 3D coordinates, several studies were selected. The coordinates were reported in either Montreal Neurology Institute (MNI) or Talairach coordinate space. Previous works which used the ALE Meta-Analysis on considered keywords were screened in order to extract more articles [YA18; Owe+05; RCM21; Keu+14; Die+12].

The final dataset (Table 2.1) consist of 61 papers containing a total of 1827 foci from 1238 subjects.

Table 2.1: Information on Source Data Sets Included in the Analysis

Author	#Foci	#Subjects
Abler et al. [Abl+09]	43	15
Aharon et al. [Aha+01]	51	6
Akitsuki et al. [Aki+03]	35	36
Beneventi et al. [BEN+07]	24	12
Carrion et al. [San+08]	34	13
Christakou et al. [Chr+09]	13	19
Cloutier et al. [Clo+08]	19	48
Cohen et al. [Coh+05]	39	16
Cox et al. [Cox05]	28	22
Croxson et al. [Cro+09]	9	19
Cruz et al. [DCr+16]	27	23
Delgado et al. [DEL+03]	12	18

Delgado et al. [Del+00]	32	9
Di et al. [DZB20]	26	49
Drobyshevsky et al. [DBS06]	13	31
Duggirala et al. [Dug+16]	62	50
Elliott et al. [Ell+04]	21	12
Elliott et al. [Ell+03]	16	12
Elliott et al. [EFD00]	19	9
Fujiwara et al. [Fuj+09]	23	17
Glascher et al. [GHO08]	20	20
Greck et al. [Gre+08]	20	15
Hauser et al. [Hau+14]	12	20
Jarcho et al. [Jar+12]	63	26
John O Doherty [ODo+03]	48	15
John O Doherty et al. [ODo+02]	18	8
Killgore et al. [Kil+03]	30	13
Kirscg et al. [Kir+03]	56	27
Knutson et al. [Knu+01b]	23	9
Knutson et al. [Knu+01a]	24	8
Knutson et al. [Knu05]	26	14
Knutson et al. [Knu+03]	21	12
Koeneke et al. [Koe+08]	33	19
Kohno et al. [Koh+14]	14	27
Koppelstaetter et al. [Kop+08]	16	15
Lawrence et al. [Law+08]	37	15
Lee et al. [Lee+13]	58	14
Nieuwenhuis et al. [Nie+05]	10	14
Nobre et al. [Nob+04]	42	10
Padilla et al. [Mir+18]	23	25
Pierce et al. [Pie+15]	19	42
Pochon et al. [Poc+02]	43	6
Rademacher et al. [Rad+10]	47	28
Reilhac et al. [Rei+13]	39	12
Rodger et al. [Lem+19]	43	22
Rogers et al. [Rog+04]	24	14
Rosell-Negre et al. [Ros+16]	11	37
Schienle et al. [Sch+09a]	12	19
Schmidt et al. [Sch+09b]	14	50
Schonberg et al. [Sch+12]	28	16
Seo et al. [Seo+12]	19	22
Sescousse et al. [SRD10]	46	18
Signe Bray and John O'Doherty [BO07]	5	23
Smith et al. [Smi+10]	54	23
Smith et al. [SMI+09]	14	25
Spreckelmeyer et al. [Spr+09]	64	32
Taylor et al. [Tay+04]	41	12

Tobler et al. [Tob+07]	19	16
Vassena et al. [Vas+14]	78	20
Winston et al. [Win+07]	15	26
Xue et al. [Xue+08]	52	13
Total: 61 papers	1827 foci	1238 Subjects

2.1.1 Reward

Humans tend to take decisions influenced by the expected reward value they obtain from different options. In order to assess that, extended fMRI studies were conducted regarding reward processing. There is plenty of evidence that suggests that different parts of the brain are preferentially activated by reliable predictors of reward [Knu+01b; Rad+10; Coh+05; Ros+16]. Either by involving choice-making in their studies [GHO08; Koe+08; Law+08; Nie+05; SRD10], or by conducting passive task [ODo+02; Aha+01; Clo+08; Sch+09a; BO07; Spr+09; Tay+04], the scientist found out that reward seems to influence the prefrontal cortex hemodynamic response.

The experiment task varied a lot between passive [Smi+10; Clo+08; Aha+01], gambling, [Aki+03; Vas+14; Xue+08] and performance-dependent [Tob+07; Spr+09; Kir+03]. A typical gambling task consists of subjects being able to choose between two simultaneously presented gambles with different probabilities of winning[Rog+04] (Figure 2.1). The performance-dependent task can be quite similar to the gamble one but one important monitored factor is also the reaction time and how fast the subject responds to the stimuli [Spr+09]. In order to study the response of the human brain to different types of stimuli, researchers created simple tasks in which subjects passively viewed different images [Win+07].

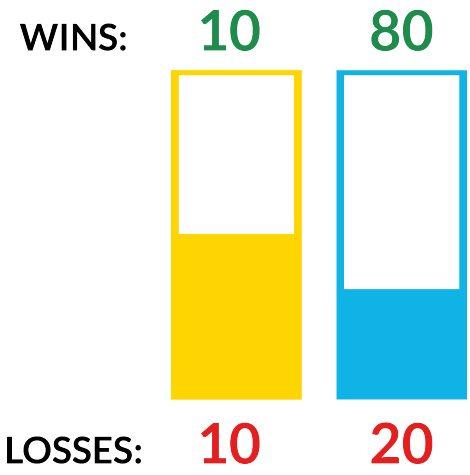

Figure 2.1: An actual task from Rodgers et al. [Rog+04]. An example of stimuli consisting in a 50% change probability of winning or losing 10 points and 2/3 chances to win 80 points and 1/3 chances to lose 20 points

In their study, [Aha+01] the authors are investigating on humans the reward values for discrete categories of beautiful faces showing that they have deferentially activated reward circuitry. Six subjects participated in an fMRI experiment which concluded that reward circuitry can be activated by passive viewing of female faces. The experiment revealed a significant effect on Nucleus Accumbens, which was more pronounced in the beautiful

female faces. After switching the analysis from the region-of-interest based (ROI-based) to a voxel-by-voxel analysis based on data averaged across the cohort (post-hoc parametric analysis) it was revealed that not one region responded in a similar fashion and that a multitude of regions produced signals.

Rosell Negre et al. [Ros+16] found in their parametric increasing reward magnitude test based on thirty-seven volunteers that improved performance in response time and accuracy terms is associated with the reward magnitude. This study correlates the activation of the left DLPFC and dorsal caudate with an opposite effect based on reward magnitude increasing.

In order to emphasize the importance of financial reward and penalty while keeping the reward magnitude constant [Aki+03] realized an experiment for guessing the color of the suit of a card based on thirty-six volunteers. The report managed to correlate the bilateral anterior cingulate and medial prefrontal cortices with winning or losing strikes. Also, DLPFC is proved to be activated when after a strike the subject manages to change the outcome thus proving that there may be a brain activity related to event-sequence context.

Seeking to establish the role of the Orbitofrontal Cortex in conditioned reward without any reward anticipation Cox et al. [Cox05] conducted an experiment with twenty-two subjects in which they were scanned while performing two separate tasks. One was a simple card game in which each visual pattern was associated with positive or negative feedback and a similar one but without showing the feedback. It was found that the negative feedback was correlated with the activation of the ventral striatum [Del+00] and OFC. An interesting fact is that in the second task the volunteers manifested activation of the same OFC regions when were presented with the stimuli that were paired with reward in the previous task. These findings correlate OFC with both context-dependent events based on acquired reward value and rewarding stimuli.

On the same idea, Delgado et al. [Del+00] tracked the hemodynamic responses to reward and punishment in the Striatum realizing an experiment where volunteers took part in a gambling task where they received punishment, neutral feedback, or monetary reward (as stimuli for correct guesses). It was concluded that parts of the dorsal and Ventral Striatum were activated when receiving a monetary incentive and deactivated following a punishment.

Christakou et al. [Chr+09] changed the Iowa Gambling Task and simplify it in order to be able to reflect participants experiences during decision making, exactly the moment of decision or the evaluation of decision outcomes. It was shown that the two prefrontal areas, the dorsolateral and right ventromedial prefrontal cortex are sensitive to accumulating negative outcomes and that these subregions drive adaptive choice in the task like shifting away from disadvantageous options.

Table 2.2: Reward Value Studies

Author	#Foci	#Subjects	Reward Phase	Reward Contingency	Reward Type
Abler et al. [Abl+09]	17	15	anticipation phase	performance-dependent	monetary reward
Abler et al. [Abl+09]	5	15	outcome phase	performance-dependent	monetary reward
Abler et al. [Abl+09]	21	15	outcome phase, anticipation phase	performance-dependent	monetary reward
Aharon et al. [Aha+01]	51	6	outcome phase	passive	social reward
Akitsuki et al. [Aki+03]	22	36	outcome phase	gambling	monetary reward
Akitsuki et al. [Aki+03]	13	36	outcome phase	gambling	monetary reward, context-dependent reward
Christakou et al. [Chr+09]	13	19	outcome phase	gambling	monetary reward
Cloutier et al. [Clo+08]	19	48	outcome phase	passive	social reward
Cohen et al. [Coh+05]	25	16	outcome phase	performance-dependent	monetary reward
Cohen et al. [Coh+05]	14	16	anticipation phase	performance-dependent	monetary reward
Cox et al. [Cox05]	28	22	outcome phase	gambling	monetary reward
Croxson et al. [Cro+09]	9	19	anticipation phase		monetary reward
Delgado et al. [DEL+03]	12	18	outcome phase	gambling	monetary reward
Delgado et al. [Del+00]	32	9	outcome phase	gambling	monetary reward
Elliott et al. [Ell+04]	21	12	outcome phase	performance-dependent	monetary reward
Elliott et al. [Ell+03]	16	12	outcome phase	performance-dependent	monetary reward
Elliott et al. [EFD00]	6	9	outcome phase	gambling	monetary reward
Elliott et al. [EFD00]	13	9	outcome phase	gambling	monetary reward, context-dependent reward
Fujiwara et al. [Fuj+09]	23	17	outcome phase	performance-dependent	monetary reward
Glascher et al. [GHO08]	20	20	outcome phase	reversal learning	monetary reward
Greck et al. [Gre+08]	20	15	outcome phase	gambling	feedback reward
Hauser et al. [Hau+14]	12	20	outcome phase	reversal learning	monetary reward
Jarcho et al. [Jar+12]	41	26	outcome phase		monetary reward
Jarcho et al. [Jar+12]	22	26	anticipation phase		monetary reward
John O Doherty [ODo+03]	6	15	outcome phase	passive	monetary reward
John O Doherty [ODo+03]	42	15	outcome phase	performance-dependent	monetary reward
John O Doherty et al. [ODo+02]	13	8	anticipation phase	passive	taste reward
John O Doherty et al. [ODo+02]	5	8	outcome phase	passive	taste reward
Killgore et al. [Kil+03]	30	13	outcome phase	passive	food photo reward
Kirscg et al. [Kir+03]	38	27	anticipation phase	performance-dependent	monetary reward
Kirscg et al. [Kir+03]	18	27	anticipation phase	performance-dependent	monetary reward, verbal reward

Table 2.3: Reward Value Studies - continuation

Author	#Foci	#Subjects	Reward Phase	Reward Contingency	Reward Type
Knutson et al. [Knu05]	26	14	anticipation phase	performance-dependent	monetary reward
Knutson et al. [Knu+01b]	10	9	outcome phase	performance-dependent	monetary reward
Knutson et al. [Knu+01b]	13	9	anticipation phase	performance-dependent	monetary reward
Knutson et al. [Knu+03]	17	12	anticipation phase	performance-dependent	monetary reward
Knutson et al. [Knu+03]	4	12	outcome phase	performance-dependent	monetary reward
Knutson et al. [Knu+01a]	24	8	anticipation phase	performance-dependent	monetary reward
Koeneke et al. [Koe+08]	5	19	anticipation phase	gambling	taste reward
Koeneke et al. [Koe+08]	28	19	outcome phase	gambling	taste reward
Kohno et al. [Koh+14]	14	27		gambling	monetary reward
Lawrence et al. [Law+08]	5	15	decision phase	gambling	monetary reward
Lawrence et al. [Law+08]	32	15	outcome phase	gambling	monetary reward
Nieuwenhuis et al. [Nie+05]	2	14	outcome phase	gambling	monetary reward
Nieuwenhuis et al. [Nie+05]	8	14	outcome phase	gambling	monetary reward, context-dependent reward
Rademacher et al. [Rad+10]	6	28	outcome phase	performance-dependent	monetary reward
Rademacher et al. [Rad+10]	15	28	outcome phase	performance-dependent	social reward
Rademacher et al. [Rad+10]	7	28	anticipation phase	performance-dependent	social reward
Rademacher et al. [Rad+10]	19	28	anticipation phase	performance-dependent	monetary reward
Rodger et al. [Lem+19]	28	22		n-back task	
Rogers et al. [Rog+04]	24	14	decision phase	gambling	monetary reward
Rosell-Negre et al. [Ros+16]	11	37	anticipation phase	performance-dependent	monetary reward
Schienle et al. [Sch+09a]	12	19	outcome phase	passive	food photo reward
Schonberg et al. [Sch+12]	11	16	outcome phase	gambling	monetary reward
Schonberg et al. [Sch+12]	17	16	decision phase	gambling	monetary reward
Sescousse et al. [SRD10]	20	18	outcome phase	performance-dependent	monetary and erotic reward
Sescousse et al. [SRD10]	20	18	outcome phase	performance-dependent	erotic reward
Sescousse et al. [SRD10]	6	18	outcome phase	performance-dependent	monetary reward
Signe Bray and John O'Doherty [BO07]	5	23	outcome phase	passive	social reward
Smith et al. [SMI+09]	14	25	anticipation phase	gambling	monetary reward
Smith et al. [Smi+10]	19	23	outcome phase	passive	social reward, monetary reward
Smith et al. [Smi+10]	14	23	outcome phase	passive	social reward
Smith et al. [Smi+10]	21	23	outcome phase	passive	monetary reward

Table 2.4: Reward Value Studies - continuation

Author	#Foci	#Subjects	Reward Phase	Reward Contingency	Reward Type
Spreckelmeyer et al. [Spr+09]	29	32	anticipation phase	performance-dependent	social reward
Spreckelmeyer et al. [Spr+09]	35	32	anticipation phase	performance-dependent	monetary reward
Taylor et al. [Tay+04]	3	12	decision phase	n-back task	monetary reward
Taylor et al. [Tay+04]	6	12	anticipation phase	n-back task	monetary reward
Taylor et al. [Tay+04]	9	12		n-back task	monetary reward
Tobler et al. [Tob+07]	19	16	anticipation phase	performance-dependent	monetary reward
Vassena et al. [Vas+14]	13	20	decision phase	gambling	monetary reward
Vassena et al. [Vas+14]	65	20	outcome phase	gambling	monetary reward
Winston et al. [Win+07]	15	26	outcome phase	passive	social reward
Xue et al. [Xue+08]	52	13	outcome phase	gambling	monetary reward

2.1.2 Working Memory

Working memory is the cognitive ability that enables humans to retain and manipulate information or the process by which the recollected stimuli are held "on-line" [96] to guide behavior when there are no external cues. In order to investigate the working memory process, one of the most used tasks is "n-back" (Figure 2.2). A typical "n-back" task involves that participants which are presented with a sequence of stimuli must recognize if the current stimulus matches another "n" trial back. The stimuli (Table 2.5) can be either numbers [San+08; Lee+13], letters [DZB20; DBS06; Mir+18; Sch+09b], words or pseudo-words [Pie+15; Rei+13], facial expressions, or scrambled drawings [BEN+07].

After collecting and analyzing the fMRI data from subjects performing the n-back task with letter stimulus on 1-back and 2-back conditions Di et al. [DZB20] arrived at a conclusion that associates signals in the anterior cingulate cortex (ACC) with increased functional communication between the frontoparietal regions [Seo+12]. Pochon et al. [Poc+02] found a higher hemodynamic response in the dorsolateral prefrontal cortex and in the lateral frontopolar areas but only for the demanding 3-back conditions. Koppelstaetter et al. [Kop+08] reached a similar conclusion, although used as a verbal stimulus when caffeine was administered, the signal extended from the dorsolateral prefrontal cortex to the right anterior cingulate cortex. Working on the same task modality Schmidt et al. [Sch+09b] couldn't differentiate different regions involved in working memory tasks for men and women.

Seeking to clarify the inconsistencies in previous findings of neuroimaging studies of letter-identity processing within strings, Reilhac et al. [Rei+13] realized an experiment with a perceptual matching task, as a variation of the "n-back" task, involving twelve

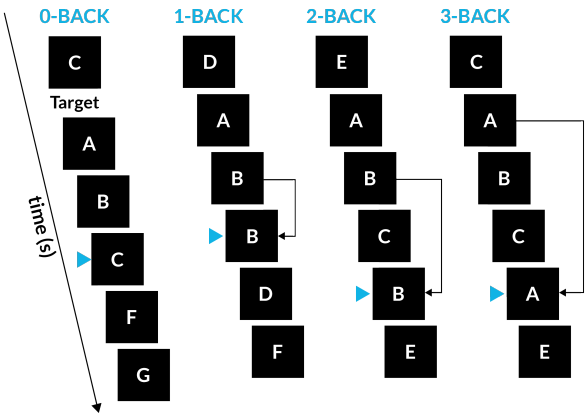

Figure 2.2: Illustration of an n-back task. In the 0-back task, the stimuli must be matched to an apriori presented number. In the 1-back, 2-back and 3-back tasks, the subjects are asked to decide if the presented cue matched the one presented one, two or three stimuli before.

skilled readers and twelve adults with developmental dyslexia. It was found brain activity in areas from the left ventral occipito-temporal (vOT) and left superior parietal lobules (SPLs) regions. However, these parts presented a lower hemodynamic response for the dyslexic participants and thus emphasizing the importance of these areas for the letter string processing.

Using an n-back task with facial expressions and scrambled drawings stimuli, Beneventi et al. [BEN+07] establish that increasing memory load yielded between other a significant activation in the prefrontal cortex. The same region was found with a hemodynamic response by Duggirala et al. [Dug+16] in all their tasks involving stimuli like words, objects and faces.

On the other hand, conducting a pioneer study involving volunteers with autism spectrum disorder (ASD) as well as normal developing control participants in order to identify functional alterations in brain functional circuitry during response shifting in ASD, Cruz et al. [DCr+16] discovered a reduced hemodynamic response for both frontal cortex and ventral striatum when choice outcome after reversal was uncertain for the ASD group.

By using event-related fMRI, Nobre et al. [Nob+04] identified the neural system responsible for directing the attention to locations in arrays held as mental representations and compared it to the system for directing attention externally. In order to isolate the brain activation, ten teen healthy volunteers participated in an experiment with intermixed trials, precue and retrocue. Using an array of four differently colored crosses preceded or followed by spatial cues (precue or retrocue), they made a delayed decision about the color of the item placed at the cued location in the array. It was found that the networks that support these two critical aspects of spatial cognition are extensively overlapping.

Table 2.5: Working Memory Studies

Author	#Foci	#Subjects	Contrast	Task Modality	Task Stimulus
Beneventi et al. [BEN+07]	24	12	2-back > 1-back > 0-back	n-back task	visual facial expression, visual scrambled drawings
Carrion et al. [San+08]	16	13	2-back > 0-back	n-back task	visual numbers
Carrion et al. [San+08]	18	13	3-back > 0-back	n-back task	visual numbers
Cruz et al. [DCr+16]	27	23	-	reversal learning task	visual identical shapes
Di et al. [DZB20]	13	49	1-back > 2-back	n-back task	visual letters
Di et al. [DZB20]	13	49	2-back > 1-back	n-back task	visual letters
Drobyshevsky et al. [DBS06]	13	31	2-back > 0-back	n-back task	visual letters
Duggirala et al. [Dug+16]	62	50	2-back > 0-back	n-back task	visual object, visual faces, visual word recognition
Koppelstaetter et al. [Kop+08]	16	15	2-back > 0-back	n-back task	verbal
Lee et al. [Lee+13]	58	14	1-back > rest	n-back task	visual numbers
Nobre et al. [Nob+04]	30	10	retrocue and precue	experimental task	visual spatial cue
Nobre et al. [Nob+04]	9	10	retrocue > precue	experimental task	visual spatial cue
Nobre et al. [Nob+04]	3	10	precue > retrocue	experimental task	visual spatial cue
Padilla et al. [Mir+18]	10	25	2-back > 0-back	n-back task	visual letters
Padilla et al. [Mir+18]	13	25	3-back > 0-back	n-back task	visual letters
Pierce et al. [Pie+15]	19	42	2-back > 1-back > 0-back	n-back task	verbal pseudo-words
Pochon et al. [Poc+02]	43	6	3-back > 2-back > 1-back > 0-back	n-back task	visual letters
Reilhac et al. [Rei+13]	21	12	sub-dif > baseline	perceptual matching task	visual word recognition
Reilhac et al. [Rei+13]	14	12	sub-dif > frame-dif	perceptual matching task	visual word recognition
Reilhac et al. [Rei+13]	4	12	sub-id > baseline	perceptual matching task	visual word recognition
Rodger et al. [Lem+19]	15	22	n-back > control task	n-back task	visual shape color
Schmidt et al. [Sch+09b]	14	50	3-back > 2-back > 1-back > 0-back	n-back task	visual letters
Seo et al. [Seo+12]	19	22	2-back > 0-back	n-back task	visual letters
Taylor et al. [Tay+04]	23	12	-	n-back task	visual shape

2.2 Meta-Analysis

2.2.1 ALE Meta-Analysis

In order to make a statistical analysis of the gathered data from the studies, an Activation Likelihood Estimation(ALE) Meta-Analysis. The aim is to perform a comprehensive analysis, including all of the reports that measure the hemodynamic response of the brain in conjunction with neuroimaging data. The key idea of the ALE algorithm is to consider the activation foci as a center of probability distribution and not in a discrete way.

The ALE Meta-Analysis was introduced in 2002 when Turkeltaub et al. [Tur+02] presented a meta-analysis of the single word reading which was verified with their own fMRI study using thirty-two subjects on the same task. At the same time, Chein et al. [Che+02] presented a meta-analysis of working memory studies with which they verified their findings in two sub-regions of the left inferior frontal cortex. In that algorithm, Gaussian probability distributions were formed around the foci obtained from collected papers. That algorithm was termed Aggregated Gaussian-Estimated Sources (AGES).

In order to make an ALE meta-analysis (Figure2.3) the MNI space was divided into $2 - mm^3$ voxels. Each foci was modeled by a three-dimensional Gaussian distribution with a computed full width at half-maximum (FWHM) [Eic+09] based on the number of subjects of each experiment. After that, the Model Activation (MA) maps are computed by merging all maps of the probability distribution of each coordinate by taking the voxel-wise union of their probability values (eq 2.3). This merge is made by taking into account the within-experiment and withing-group effect [Tur+11], using the maximum probability associated with one focus instead of their addition, which limits the possibility of multiple coordinates from one experiment to jointly influence the MA maps and thus the ALE MAP. Thus, the MA can be considered a summary of the results reported in an experiment/group experiment taking into account the spatial uncertainties of the reported foci [Eic+12]. Finally, the ALE map (eq 2.4) is created by computing the union of all the MA maps.

$$E_i(k,l,m) = \sum_{p=1}^{F_i} B_p(k,l,m), i \in \{1,N\} \tag{2.1}$$

$$PD_p(k,l,m) = G_{3D,S_i} * B_p(k,l,m), p \in \{1,F_i\} \tag{2.2}$$

$$MA_i(k,l,m) = \max_i(PD_p(k,l,m)), p \in \{1,F_i\}, i \in \{1,N\} \tag{2.3}$$

$$ALE = 1 - \prod_{i=1}^{N}(1 - MA_i) \tag{2.4}$$

where:
(k,l,m) are the dimensions of the brain in the MNI space. $k \in \{0,91\}$, $l \in \{0,109\}$ and $m \in \{0,91\}$
N is the number of experiments
F_i is the number of foci of the experiment i
S_i is the number of subjects of the experiment i
E_i is the binary map of the experiment i having value 1 at each reported coordinate and 0 otherwise
$B_p(k,l,m)$ is the binary map of each foci p in a experiment having 1 at the reported coordinate and 0 otherwise
$PD_p(k,l,m)$ is the probability distribution map for each foci p
G_{3D,S_i} is the three-dimensional Gaussian kernel with a computed FWHM based on the number of subjects of the respective experiment
$MA_i(k,l,m)$ is the model activation map of experiment i
ALE is the activation likelihood estimation map

A cluster-level inference in order to address the family-wise error rate correction was applied [Eic+12; Eic+16]. A threshold of p=0.001 was chosen as the cluster-forming threshold for the analysis. Using this value, the first step is to threshold the statistical image of uncorrected voxel-wise p-values. A set of random experiments with the same characteristics present in real data are simulated. The p-value for each cluster is given by the cluster that arises from random data and is bigger than the actual cluster. If in the end,

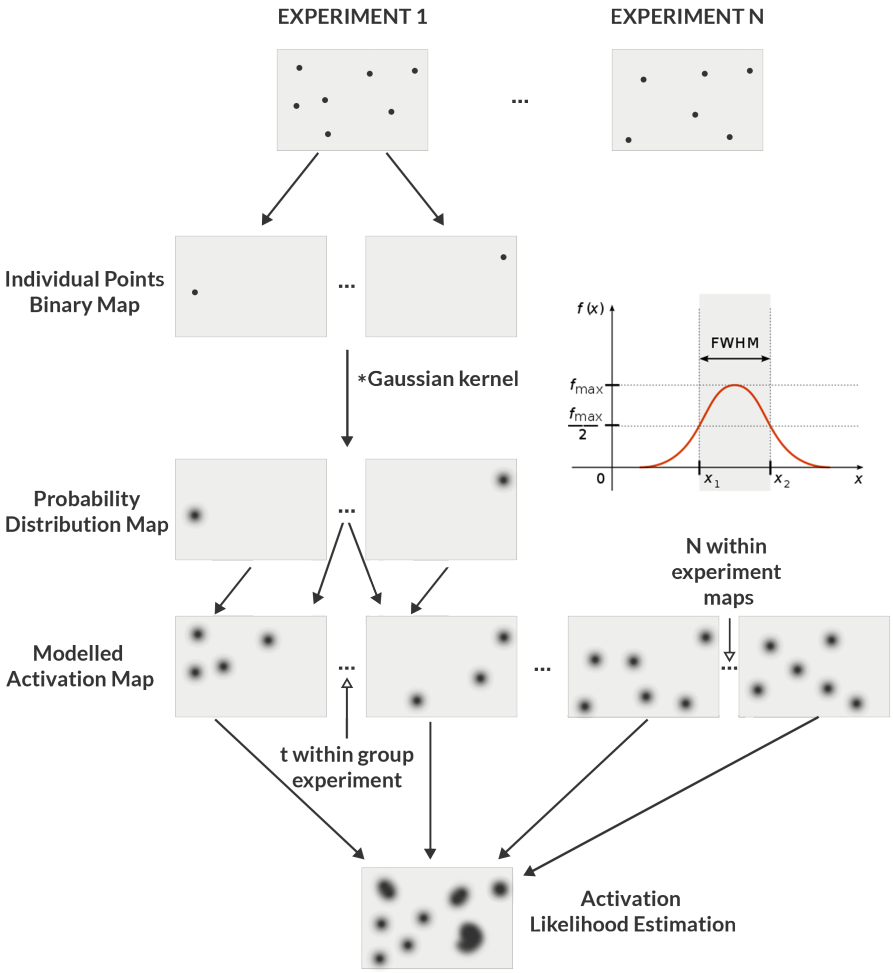

Figure 2.3: Activation Likelihood Estimation Meta-Analysis pipeline

that number is smaller than the threshold they are discarded. This correction method was proved to be the most appropriate to use for statistical inference [Eic+16], over for example voxel-level one which is way more conservative.

Using this corrected algorithm for ALE meta-analysis it is possible to give an approximation of the likelihood that a given coordinate can be truly activated during an experiment.

In the following reports, for the brain areas, FSLMATHS and ATLASQUERY with "MNI Structural Atlas" were used in order to calculate the center of gravity of the contiguous groups of voxels, the CLUSTER tool from the FSL version 6.0.5.2 [UK22] was used. In order to do the analysis, all the Talairach coordinates were converted to MNI using the Lancaster et al.[Lan+07] transformation algorithm implemented in the project utility package.

Group by experiment - "n-back" task with "visual" stimuli

The ALE analysis for the "n-back" task realized using visual stimuli, based on 12 papers consisting of 20 tables with 354 foci, showed a network that was distributed over the frontal, occipital and parietal lobes (Table 2.6). This analysis involves the biggest number of clusters with high significance, showing that the working memory network is rather complex and widespread involving most parts of the brain (Figure 2.4).

Table 2.6: Significant clusters for selection - "n-back" task with "visual" stimuli

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Caudate, Frontal Lobe, Insula, Occipital Lobe, Parietal Lobe, Putamen	11	560	2.33	1.69	19.2	46.1
	10	430	2.33	-37.7	-52.9	46.2
	9	318	2.33	-27.7	2.23	53.1
	8	272	2.33	-31.2	22.6	-1.33
	7	233	2.33	31.3	5.18	54.4
	6	206	2.33	-36.7	51.5	5.6
	5	173	2.33	-44.4	6	28.1
	4	153	2.33	44.1	-47.2	44
	3	128	2.33	32.7	22.8	-1.55
	2	100	1.88	-22.5	-66.4	44.7
	1	96	1.88	39.4	43.9	20.3

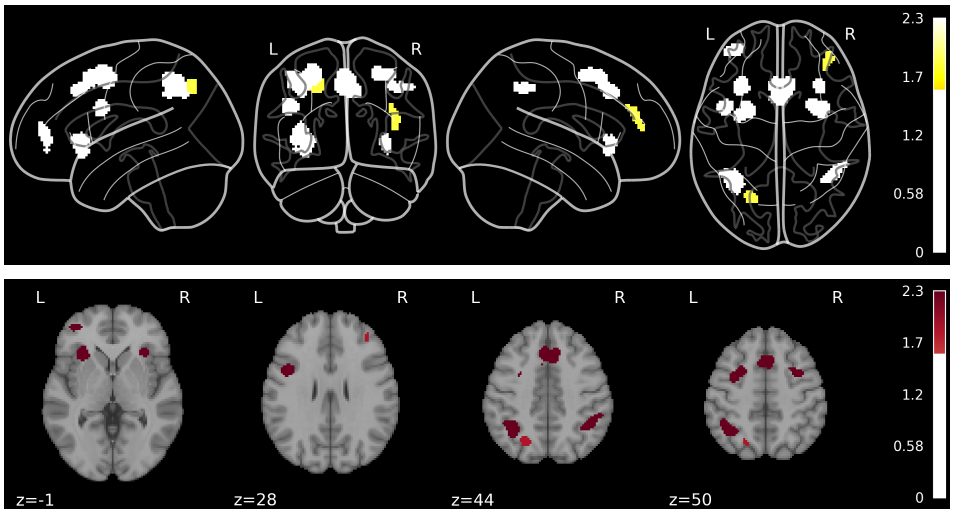

Figure 2.4: Significant clusters from the Activation Likelihood Estimation Meta-Analysis regarding the working memory "n-back" task for $p < 0.05$ corrected. On top is the z-map using a glass brain and down are the axial sections for different values of z. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

Group by experiment - contrast "Reward > No Reward" in the anticipation phase

For this group meta-analysis of "Reward > No Reward" contrast in the anticipation phase, a total of 8 Papers including 10 tables with 118 foci were used. A network involving the frontal and temporal lobes, caudate head, putamen and thalamus was revealed (Table 2.7). The presence in the frontal lobe is in line with the role of this brain part in reward prediction [Kir+03; Koe+08; Knu+01a]. Also, it can be observed that the network extends in both hemispheres (Figure 2.5).

Table 2.7: Significant clusters for contrast "Reward > No Reward" in the anticipation phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Caudate,Frontal Lobe,	3	1018	2.33	2.07	5.21	-2.77
Insula,Putamen,	2	116	2.05	40.3	20.2	-8.26
Temporal Lobe,Thalamus	1	81	1.64	6.47	21.8	35.3

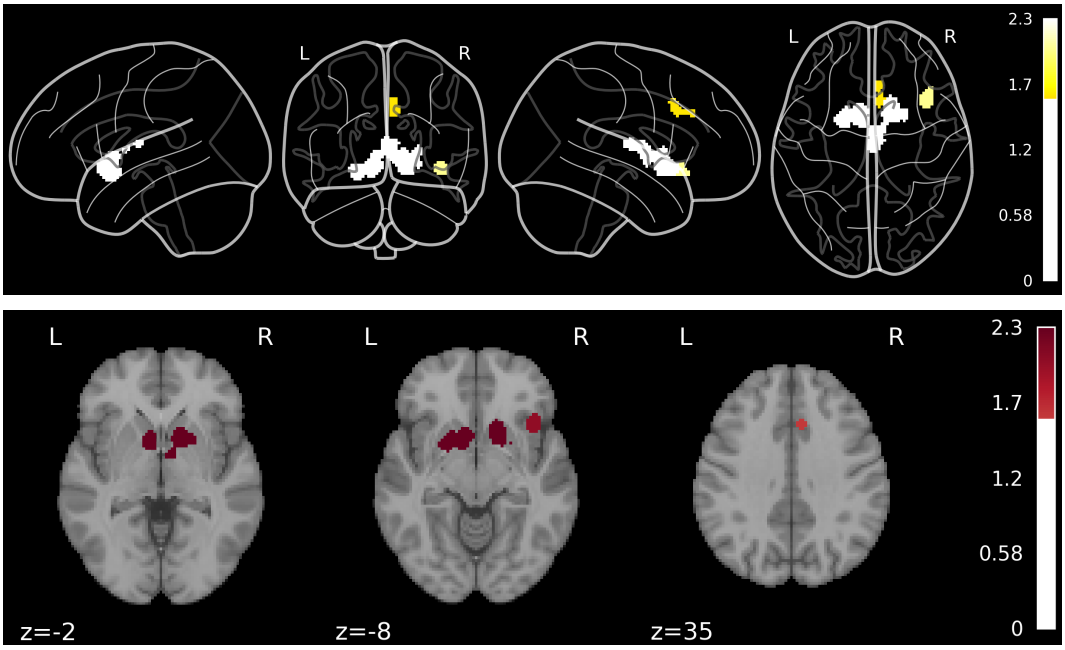

Figure 2.5: Significant clusters from the Activation Likelihood Estimation Meta-Analysis for contrast "Reward > No Reward" in the anticipation phase, $p < 0.05$ corrected. On top is the z-map using a glass brain and down are the axial sections for different values of z. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

Group by experiment - contrast "High reward > Low reward" in the anticipation phase

Using 8 Papers with 13 tables and 152 foci, a meta-analysis for "High reward > Low reward" contrast in the anticipation phase was realized, revealing a network formed by 4 significant clusters (Figure 2.6) ($p<0.05$) extending in frontal and temporal lobes, caudate head, putamen and thalamus (Table 2.8). It can be observed the similarities with the ALE meta-analysis of "Reward > No Reward" contrast in the anticipation phase. These similarities will be highlighted by the conjunction analysis performed later.

Table 2.8: Significant clusters for contrast "High reward > Low reward" in the anticipation phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Caudate,Frontal Lobe, Putamen,Temporal Lobe, Thalamus	4	431	2.33	-11.7	8.72	-2.62
	3	338	2.33	12.7	10.7	-3.91
	2	110	2.05	2.67	25	28.5
	1	93	2.05	-20.1	-14.9	-14.3

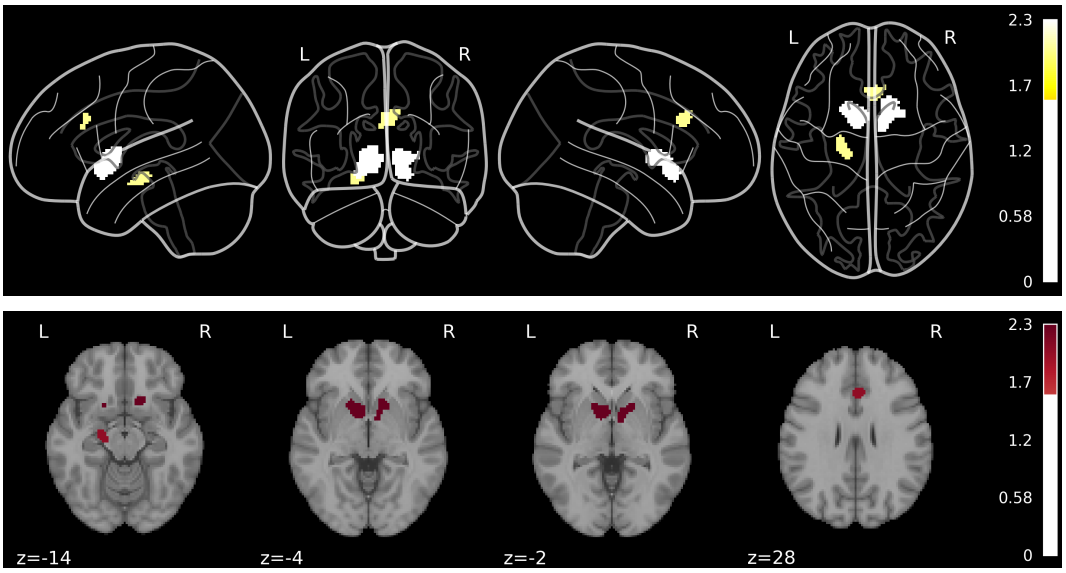

Figure 2.6: Significant clusters from the Activation Likelihood Estimation Meta-Analysis for contrast "High reward > Low reward" in the anticipation phase, $p < 0.05$ corrected. On top is the z-map using a glass brain and down are the axial sections for different values of z. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

Group by experiment - contrast "Win > Lose" in the outcome phase

A meta-analysis of 6 papers with 7 tables and 121 foci for "Win > Lose" contrast in the outcome phase was realized, revealing a zone of interest that extends in the frontal lobe, caudate head and putamen (Table 2.9) ($p<0.05$). It can be observed that the network is centered in the right hemisphere (Figure 2.7).

Table 2.9: Significant clusters for contrast "Win > Lose" in the outcome phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Caudate,Frontal Lobe,Putamen	1	99	1.75	16.1	11.6	-7.21

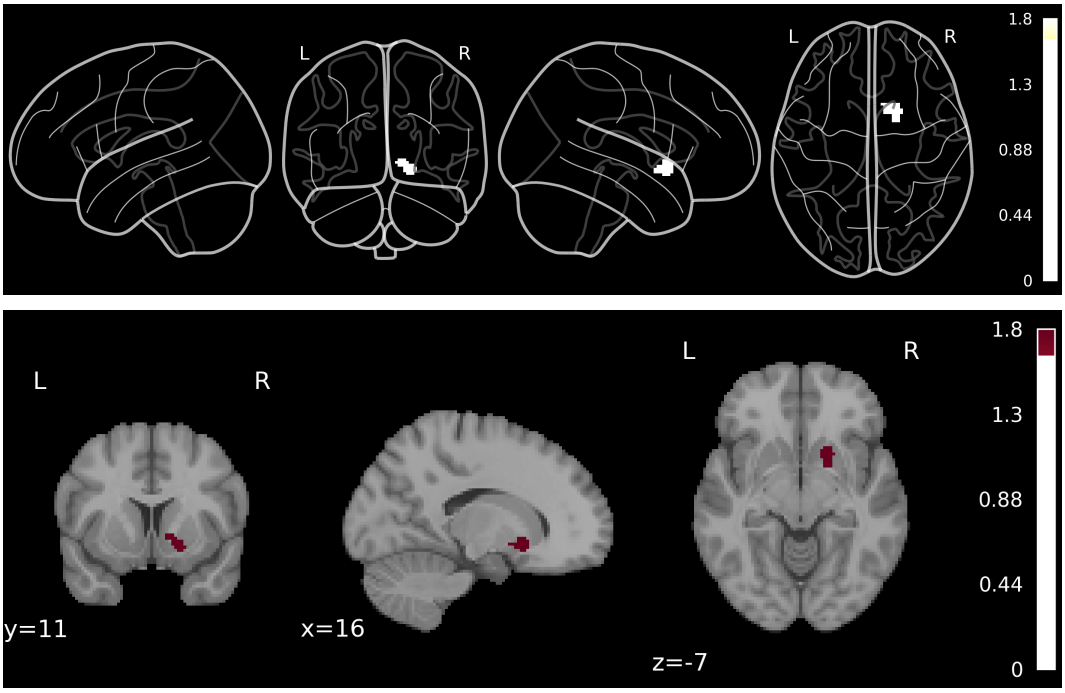

Figure 2.7: Significant clusters from the Activation Likelihood Estimation Meta-Analysis for contrast "Win > Lose" in the outcome phase, $p < 0.05$ corrected. On top is the z-map using a glass brain and down are the coronal, sagittal and axial sections of the chosen center. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

Group by experiment for Decision Making in the outcome phase

A more broad meta-analysis in the outcome phase for 22 Papers with decision-making tasks including 63 tables with 626 foci was realized. A network extending in the frontal and temporal lobes, caudate head, insula and thalamus was uncovered (Table 2.10) extending in both hemispheres (Figure 2.8).

Table 2.10: Significant clusters for Decision Making in the outcome phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Caudate,Frontal Lobe, Insula,Putamen, Temporal Lobe,Thalamus	4	440	2.33	-14.1	9.47	-5.52
	3	245	2.33	-1.34	49.6	-7.41
	2	230	2.33	15.2	11.6	-3.03
	1	168	2.33	32.7	25.4	-2.19

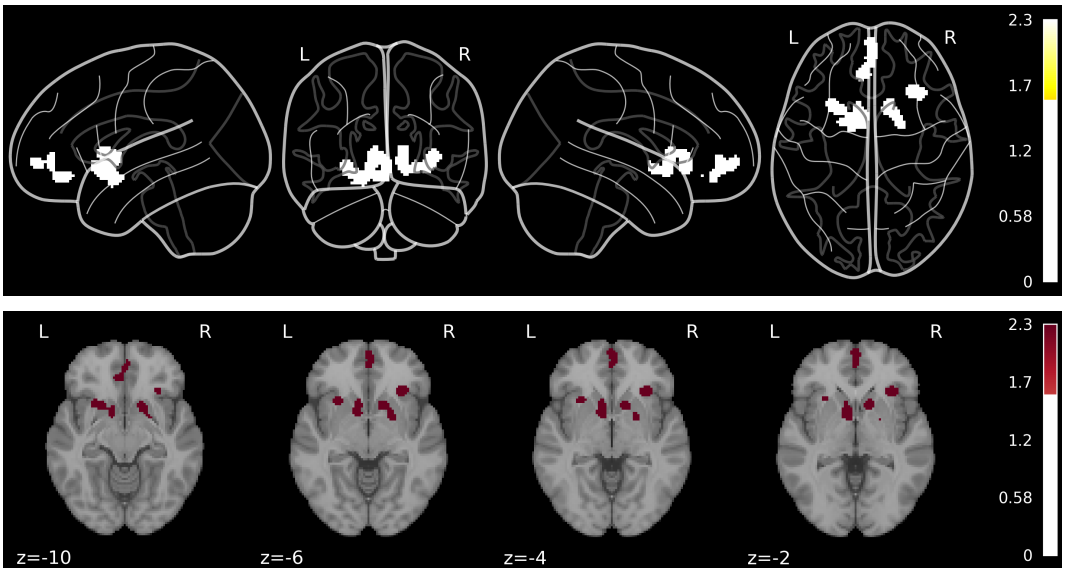

Figure 2.8: Significant clusters from the Activation Likelihood Estimation Meta-Analysis for Decision Making in the outcome phase, $p < 0.05$ corrected. On top is the z-map using a glass brain and down are the axial sections for different values of z. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

Group by experiment for Decision Making in the anticipation phase

We performed an ALE meta-analysis of 7 Papers with 18 tables and 123 foci for decision-making tasks taking into consideration just the anticipation phase. The result revealed the network extending in the temporal lobe, thalamus, caudate head and putamen (Table 2.11). In this case, the network can be observed to be centered in the left hemisphere (Figure 2.9).

Table 2.11: Significant clusters for Decision Making in the anticipation phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Caudate,Putamen,	2	150	2.33	-9.57	6.53	1.19
Temporal Lobe,Thalamus	1	110	2.05	-19.2	-14.3	-15.2

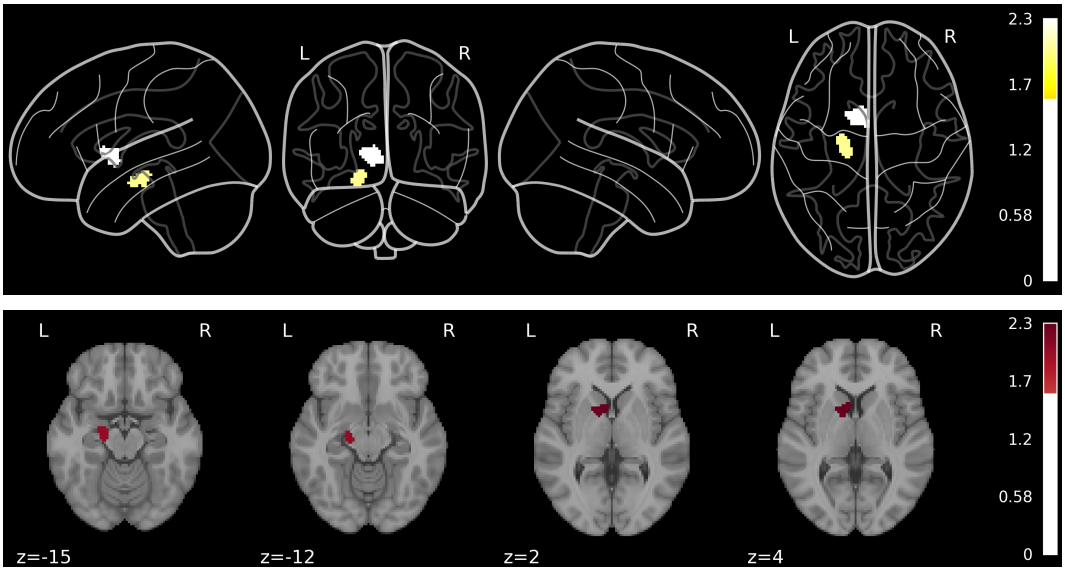

Figure 2.9: Significant clusters from the Activation Likelihood Estimation Meta-Analysis for Decision Making in the anticipation phase, $p < 0.05$ corrected. On top is the z-map using a glass brain and down are the axial sections for different values of z. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

2.3 Conjunction analysis

The overlap of the ALE meta-analysis results was analyzed using the AND conjunction null hypothesis presented by Nichols et al. [Nic+05].

Conjunction analysis between decision making and "Win > Lose" in the outcome phase and "Reward > No Reward" and "High > Low Reward" in the anticipation phase

A conjunction analysis across the "Reward > No Reward" and "High > Low Reward" in the anticipation phase with "Win > Lose" and decision making in the outcome phase was conducted in order to assess to what extent the consequence network was modulated by being rewarded with a high incentive in a decision making task. Results of this conjunction are edifying for this thesis showcasing a substantial overlap in the map (Table 2.12) over the prefrontal cortex [Knu+01a; Knu05; Spr+09; Abl+09]. In this case, the cluster is centered in the right part of the prefrontal cortex (Figure 2.10), an area known for its involvement in executive functioning, its ability to distinguish between right and wrong, better and poorer outcomes, future consequences of current activities, prediction of outcomes.

Table 2.12: Conjunction analysis between decision making and "Win > Lose" in the outcome phase and contrasts "Reward > No Reward" and "High > Low Reward" in the anticipation phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Caudate,Frontal Lobe,Putamen	1	46	2.33	13.9	12.9	-6.13

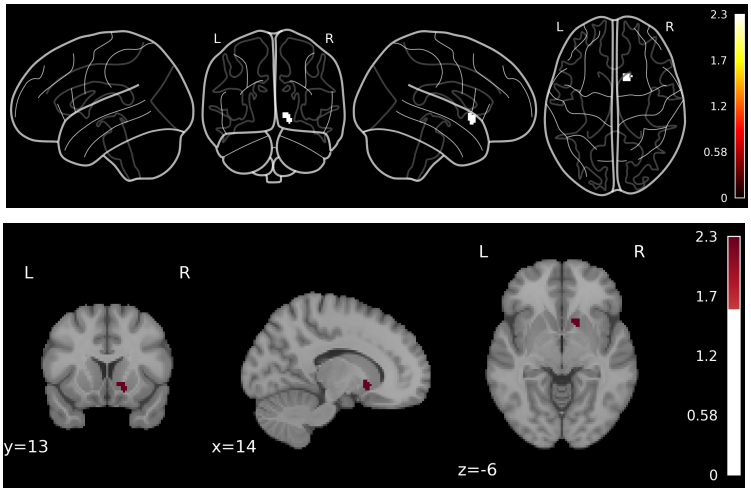

Figure 2.10: Significant cluster for conjunction analysis between decision making and "Win > Lose" in the outcome phase and contrasts "Reward > No Reward" and "High > Low Reward" in the anticipation phase, $p < 0.05$. On top is the z-map using a glass brain and down are the coronal, sagittal and axial sections of the chosen center. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

Conjunction analysis between decision making in anticipation and outcome phases and contrasts "Reward > No Reward" and "High > Low Reward" in the Anticipation phase

A conjunction analysis across the contrast "Reward > No Reward" and "High > Low Reward" in the anticipation phase, and decision-making in both anticipation and outcome phases revealed a consistent activation in the caudate and thalamus (Table 2.13). This finding is in line with reports made by Abler et al.[Abl+09], Rosell-Negre et al. [Ros+16], and Tobler et al. [Tob+07]. The tables containing all involved papers can be found in the supplementary material. It can be observed that the cluster is centered in the left hemisphere (Figure 2.11), opposite to the previous conjunction which was centered in the right hemisphere (Figure 2.10). This finding show different zone to be activated when the "Win > Lose" contrast in the outcome phase is taken into consideration.

Table 2.13: Significant clusters for conjunction analysis between anticipation and outcome phases decision making and contrasts "Reward > No Reward" and "High > Low Reward" in the Anticipation phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Caudate,Thalamus	1	55	2.33	-8	5.31	-1.24

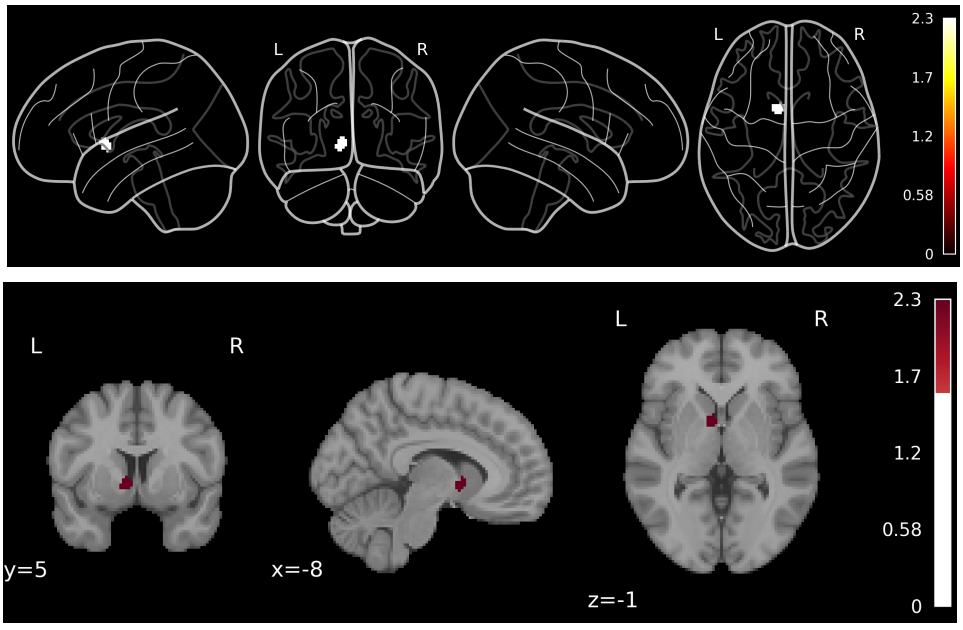

Figure 2.11: Significant cluster for conjunction analysis between anticipation and outcome phases decision making and contrasts "Reward > No Reward" and "High > Low Reward" in Anticipation phase, $p < 0.05$. On top is the z-map using a glass brain and down are the coronal, sagittal and axial sections of the chosen center. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

Conjunction analysis between working memory for "n-back task" and visual stimuli and decision making in the outcome phase

Another interesting result is given by the conjunction analysis between working memory for the "n-back task" and visual stimuli and decision making in the outcome phase. A network was revealed in the frontal lobe, insula and putamen (Table 2.14) which correlates the working memory to the reward-based decision making.

Table 2.14: Significant clusters for conjunction analysis between working memory for "n-back task" and visual stimuli and decision making in the outcome phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Frontal Lobe,Insula,Putamen	2	74	2.33	32.9	24.2	-1.22
	1	17	2.33	-29.6	18.6	-4.47

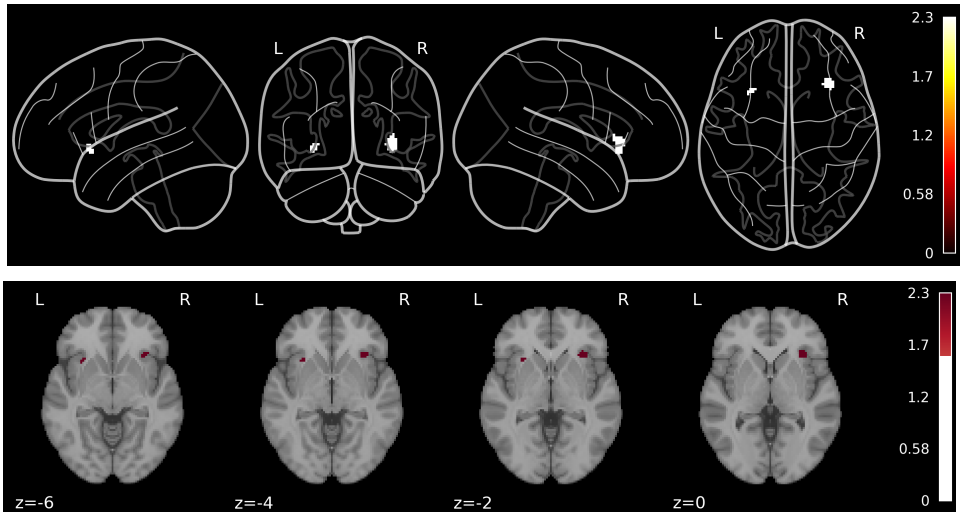

Figure 2.12: Significant clusters for conjunction analysis between working memory for "n-back task" and visual stimuli and decision making in the outcome phase, $p < 0.05$. On top is the z-map using a glass brain and down are the axial sections for different values of z. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

Conjunction analysis between working memory for "n-back task" and visual stimuli and decision making in the decision phase

In the same manner, an interesting result is given by the conjunction analysis between working memory for the "n-back task" and visual stimuli and decision making in the decision phase. A network was revealed in the frontal lobe, insula and putamen (Table 2.15) which correlates the working memory to the reward-based decision making. It can be observed that the cluster is centered in the right hemisphere (Figure 2.13).

Table 2.15: Significant clusters for conjunction analysis between working memory for "n-back task" and visual stimuli and decision making in the decision phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Frontal Lobe,Insula,Putamen	1	61	1.75	32.3	23.8	1.41

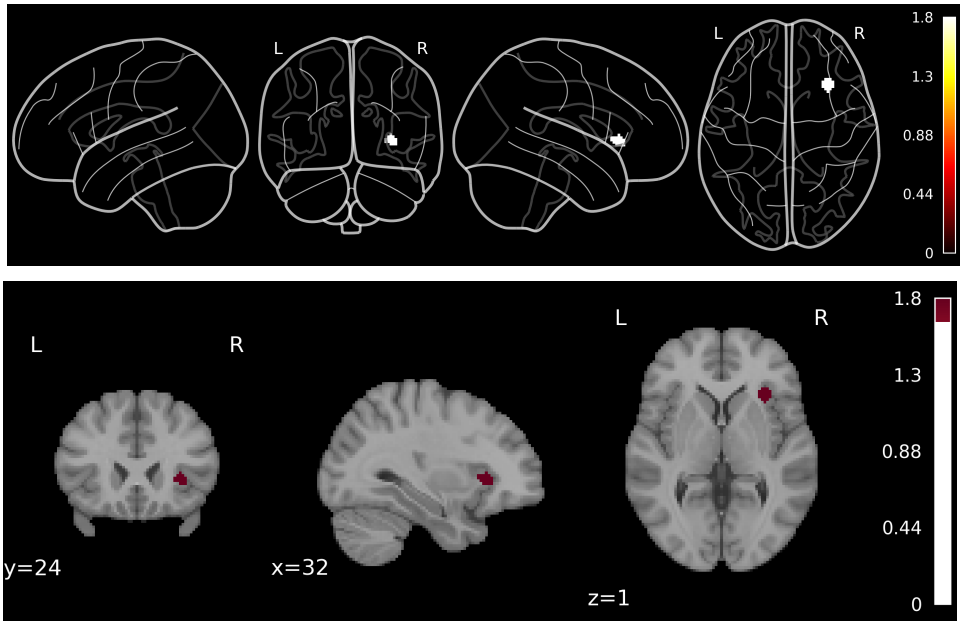

Figure 2.13: Significant clusters for conjunction analysis between working memory for "n-back task" and visual stimuli and decision making in the decision phase, $p < 0.05$. On top is the z-map using a glass brain and down are the coronal, sagittal and axial sections of the chosen center. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

Conjunction analysis between decision making in the decision phase and contrasts "Reward > No Reward" and "High > Low Reward" in the anticipation phase

A conjunction analysis between decision making in the decision phase and contrasts of "Reward > No Reward" and "High > Low Reward" in the anticipation phase was realized. A network was revealed in the frontal lobe (Table 2.16), more exactly in the Paracingulate Gyrus and Cingulate Gyrus according to the Harvard-Oxford Cortical Structural Atlas. This network correlates the decision making decision phase to the anticipation of a high reward. It can be observed that the cluster is centered in the right hemisphere (Figure 2.14).

Table 2.16: Significant clusters for conjunction analysis between decision making in the decision phase and contrasts "Reward > No Reward" and "High > Low Reward" in the anticipation phase

Brain Areas	Cluster Index	#Voxels	z-score	COG X (mm)	COG Y (mm)	COG Z (mm)
Frontal Lobe	1	8	1.64	5.5	27	32

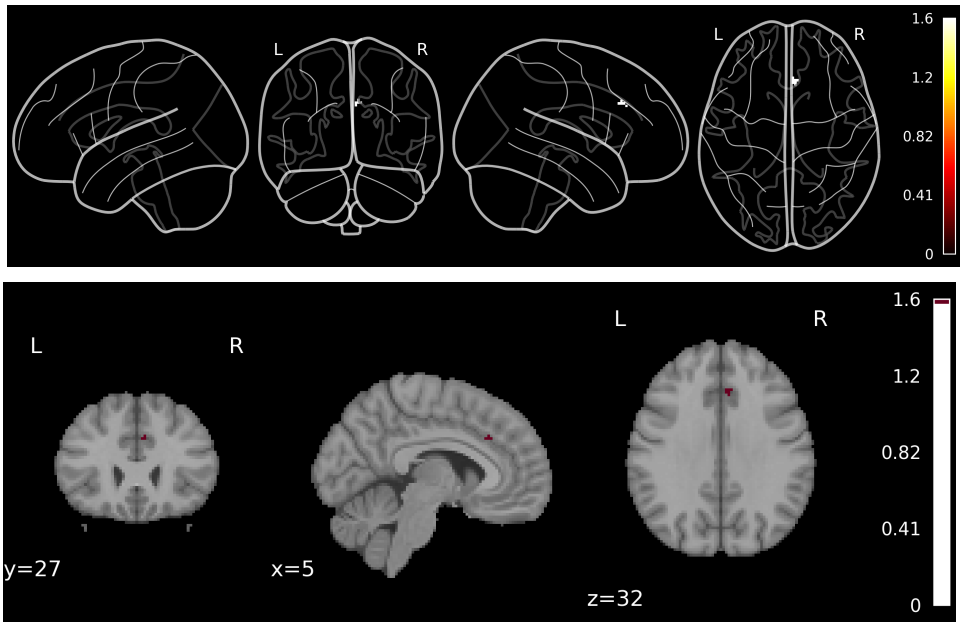

Figure 2.14: Significant clusters for conjunction analysis between decision making in the decision phase and contrasts "Reward > No Reward" and "High > Low Reward" in the anticipation phase, $p < 0.05$. On top is the z-map using a glass brain and down are the coronal, sagittal and axial sections of the chosen center. The maps are displayed using MNI152 Nonlinear Template in MNI reference space and the values are for z-score one-tailed

The code used to generate the results together with all the results which were not included in the current work can be found in the supplementary materials at [Mol22].

Chapter 3

Conclusion

3.1 Conclusion

This study aimed to identify the consistent brain network connecting the neural centers of consequence. This type of network can be derived from quantitative meta-analytic techniques for fMRI such as Activation Likelihood Estimation, multi-kernel density analysis and similar approaches, methods that have been used extensively in the last years by researchers in the neuroimaging community. An ALE meta-analysis was conducted which made possible to give an approximation of the likelihood that a given coordinate can be truly activated during an experiment. Finally, the specificity of the consequence network was tested by comparing the results of the meta-analysis for working memory, reward value and decision-making in different phases.

Consistent regional activation in the prefrontal cortex was found during the reward anticipation phase (Figure 2.5) in a cluster centered in the right hemisphere more specifically in the Right Insula (center: x=40.3; y=20.2; z=-8.26 in MNI reference space (Table 2.7)) which is in line with the general role of this brain region [Kir+03; Koe+08; Knu+01a] that this region is carrying reward-related decision signals. In the same region, significant area activation centered in the right hemisphere (center: x=12.7; y=10.7; z=-3.91 in MNI reference space (Table 2.8)) was found for "high vs low reward" gain cues. When it comes to reward processing, the meta-analysis of the "Win vs Lose" contrast in the outcome phase revealed a zone of interest that extends to the frontal lobe, caudate and putamen, centered in the right hemisphere (Figure 2.7) (center: x=16.1; y=11.6; z=-7.21 in MNI reference space (Table 2.9)).

Conjunction analysis for decision making in the outcome phase $\cap$ "Win > Lose" in the outcome phase $\cap$ "Reward > No Reward" in the anticipation phase $\cap$ "High > Low Reward" in the anticipation phase identified a cluster centered in the right hemisphere (center: x=13.9; y=12.9; z=-6.13 in MNI reference space (Table 2.12)). This conjunction was conducted in order to assess to what extent the consequence network was modulated by being rewarded with a high incentive in a decision-making task. Another conjunction of interest for decision making in the anticipation phase $\cap$ decision making in the outcome phases $\cap$ contrasts "Reward > No Reward" in the anticipation phase $\cap$ "High > Low

Reward" in the anticipation phase argues in favor of neural center of consequence located in the caudate possibly complemented by the thalamus, this time centered in the left hemisphere (center: x=-8; y=5.31; z=-1.24 in MNI reference space (Table 2.13)).

When taking into consideration the decision phase, in which different reward options are considered and motor responses are used to implement the chosen options, in conjunction with the contrast of "Reward > No Reward" and "High > Low Reward" in the anticipation phase, a network was revealed in the Paracingulate Gyrus and Cingulate Gyrus according to the Harvard-Oxford Cortical Structural Atlas which are in the frontal lobe (Figure 2.14). This network correlates the decision making decision phase to the anticipation of high reward and is centered in the right hemisphere (center: x=5.5; y=27; z=32 in MNI reference space (Table 2.16)).

This study describes the functional anatomy of contingency detection in the human brain by integrating hemodynamic centers resulting from fMRI processing techniques and meta-analysis techniques.

3.2 Future work

First, one of the current study limitations is given by the included studies. After an extensive search in the literature, only 17 studies for working memory were included of which 3 consist of decision-making tasks. This lack of papers reporting foci for this specific task didn't allow to realize a proper correlation between reward-based decision making and working memory involving decision making. Incorporating more papers and attempting to analyze the topic could be one way to go forward. It was proved that there must be at least 20 experiments in an ALE meta-analysis[Eic+16] in order to achieve valid results.

A further limitation is represented by the fact that this study started from the centers of activation areas, which are contiguous clusters of different sizes, which here are processed by using a three-dimensional Gaussian distribution with a computed full width at half-maximum (FWHM) [Eic+09] based on the number of subjects in each experiment. Another approach would be to vary the kernel by which the peak activation coordinates are modeled. A possible solution would be to apply the Seed-based d Mapping (SDM) [Rad+22] method and try their approach using the anisotropic kernels. This method can also take into account, in their effect size map, the t-values reported in individual studies which should lead to fundamentally different results than those presented here.

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