Neural Areas of Activation During Feedback Processing of Clinical Decision Making

By

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We acknowledge and respect the lək̓ʷəŋən peoples on whose traditional territory the university stands and the Songhees, Esquimalt and W̱SÁNEĆ peoples whose historical relationships with the land continue to this day.

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Abstract

Studies in neural areas of activation during clinical reasoning and decision-making play a critical role in improving medical education; however, the effect of feedback processing in clinical decision-making is poorly understood. In particular, differences in feedback processing in novice and expert clinicians during clinical decision-making. To understand this difference, we presented feedback (correct/incorrect diagnosis) to novice and expert clinicians after diagnosing simple or complex (easy, hard) cases while functional magnetic resonance imaging (fMRI) data were collected. Sixteen clinical cases (in the field of gastroenterology) were presented in the form of multiple-choice questions during an fMRI scanning session, followed by corrective feedback.

As hypothesized, providing feedback for clinical diagnosis evoked multiple neural activations in some cortical regions, including the cingulate cortex, temporal cortex, striatum, orbitofrontal, and occipital cortexes in novice and expert groups. Interestingly, our findings indicate that positive feedback evoked more significant neural activation (in areas like the temporal cortex, cingulate cortex, and striatum) in novice clinicians than experts, which suggests that the novice group relies more on motivation, reward processing, and working memory than experts. Our neuroimaging results also showed a considerable activation of the left orbitofrontal cortex in feedback processing (both positive and negative) for both groups. This area plays an active role in learning and decision-making. In sum, the results here show that feedback processing in clinicians is impacted by expertise – there are some common neural regions related to learning and decision-making. Still, there were unique activations in novices tied to motivation, reward processing, and working memory, presumably driven by their lack of experience.

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Acknowledgments

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Dedication

Special gratitude to my loving parents, whose encouragement always rings in my ears. I wholeheartedly dedicate this thesis to my lovely wife, Romina, who has been a constant source of love, support, and encouragement during graduate school and life challenges.

Abbreviations

Analysis of Variance (ANOVA)

Blood Oxygen Level Dependent (BOLD)

Dorsolateral Prefrontal Cortex (DLPFC)

Dual Processing Theory (DPT)

Electroencephalogram (EEG)

functional Magnetic Resonance Imaging (fMRI)

Field of View (FOV)

General linear model (GLM)

Gradient Recalled Echo, Echo Planar Imaging (GRE_EPI)

Long Term Memory (LTM)

Multiple Choice Questions (MCQ)

Montreal Neurological Institute (MNI)

Magnetic Resonance Imaging (MRI)

Medial Temporal Lobe (MTL)

Orbitofrontal Cortex (OFC)

Prefrontal Cortex (PFC)

Radiofrequency (RF)

Region of Interest (ROI)

Echo Time (TE)

Repetition Time (TR)

Ventrolateral Prefrontal Cortex (VLPFC)

Working Memory (WM)

Chapter 1: General Introduction

Overview

Feedback can be defined as the information provided to fill the gap between what is learned and what is supposed to be learned, which can be accomplished by increasing effort, motivation, or engagement (Hattie et al., 2007; Sadler, 1989). The gap could be reduced by restructuring the learned structures, providing guiding information to students, and introducing new methods to understand particular concepts. In a review study by Winne and Butler (1994), it is suggested that feedback can be defined as the information which helps a learner to confirm, add to, overwrite, tune, or restructure memory information.

Feedback in healthcare education can be described as the information provided to compare a learner's observed performance and a standard performance (Burgess et al., 2020). As a significant part of the learning process, feedback aims to narrow the gap between observed and expected performance by providing the learner with information to assess their performance.

Research in medical education has aimed to discover the neurocognitive processes of clinical decision-making using indirect and non-invasive imaging methods. The core research question in this field has been the effect of experience and medical education on students learning and how feedback affects the learning process. Some neuroimaging studies (Hruska et al., 2015) use functional magnetic resonance imaging (fMRI) to investigate the medical reasoning and decision-making processes and the effect of feedback on the learning process. There are different types of tasks in the literature for studying medical decision-making. Some are visuospatial/ diagnostic imaging tasks (Melo et al., 2011; Bahrami et al., 2014), tasks that explore the brain regions involved with decision-making in different cognitive states (Durning et al., 2014), and tasks that target the analytic and non-analytic decision making.

Some studies suggest a significant role of memory structures in decision-making and feedback processing. It might be the case that the common ground for feedback processing, and decision-making, is memory structures. Therefore, looking at decision-making and feedback processing from a memory perspective can help us answer the questions in the field. WM, in general, could be defined as a memory structure containing some information for a short period, facilitating decision-making and feedback processing. On the other hand, any requested information could be retrieved from long-term memory, where the bulk of brain information is stored for an extended period. Some brain regions – e.g., MLT and PFC - are thought to be associated with working memory and decision-making. In this neuroimaging study, we want to tease out any brain regions involved with feedback processing in clinical decision-making that could be engaged with some memory structures. (Heit et al., 2012; Hruska et al., 2015; Sub et al., 2002; Ruff, 2003; Goel et al., 2007; Lee et al., 2007)

Study objectives

The primary purpose of this study was to determine the neural areas of activation in feedback processing of clinical decision-making using three modifiers, clinician level of expertise, type of feedback, and task difficulty. There were two core objectives in our study. First, to determine neural areas of activation during feedback processing in two groups, novice and expert clinicians. Our second objective was to determine whether the difficulty of clinical cases (easy vs. hard questions) and the type of feedback cause different neural activation during feedback processing.

Overview of clinical decision making

First, it is worth mentioning that clinical reasoning and clinical decision-making are two different terms with different meanings in the literature. In this study, we use clinical decision-making to refer to the participant's performance/action of reasoning in making the final decision.

Performance observation, pattern recognition theory, and dual-processing theory are some main study methods in clinical decision-making. Performance observation tends to explore different stages of decision-making. As a result of those studies, some definitions and representations of decision-making were introduced (McLaughlin et al., 2006). Another popular method is pattern recognition which in clinical decision-making studies is one of the main methods of knowledge retrieval. It is considered the process of comparing symptoms to previous examples (Hruska et al., 2015; Schmidt, 1990). Another method is the dual-processing theory, where the combination of the non-analytic (type 1 decision-making) and analytic (type 2 decision-making) approaches is investigated (Evans et al., 2013; Croskerry, 2009)

Feedback processing in clinical decision making.

Feedback in healthcare education can be described as the information provided to compare a learner’s observed performance and a standard performance (Burgess et al., 2020). As a significant part of the learning process, feedback aims to narrow the gap between observed and expected performance by providing the learner with information to assess their performance. Feedback facilitates the learning process in three ways: information about students’ progress, addressing students' learning needs, and motivating students to participate in particular learning activities.

Feedback in healthcare education

Feedback can impact the learning process either positively or negatively. Evidence shows (Hattie et al., 2007) that despite the significant influence of feedback on the learning process, the type of feedback, positive or negative, and how it is presented can be differentially effective. Feedback can facilitate the learning process by providing information about the task. Therefore, it can fill the gap between what is learned and what is supposed to be learned by increasing effort, motivation, and engagement among learners (Sadler, 1989). Some cognitive processes can help to reduce the gap mentioned above, including restructuring previous information stored in the brain, assisting the learners in verifying their understanding, indicating directions for students to pursue, and introducing alternative strategies to learn particular concepts. In a review study by Winne and Butler (1994), it is suggested that feedback can be defined as the information which helps a learner to confirm, add to, overwrite, tune, or restructure memory information.

Levels of feedback processing in clinical decision making

There are some studies (Hattie et al., 2016) suggesting four levels for the influences of feedback processing, including feedback about:

- the task (FT),
- processing of task (FP),
- self-regulation (FR),
- a person itself (FS).

First, feedback can be about a task, as to whether a doctor’s diagnosis is correct or incorrect. The second level of feedback influence aims at completing a task. This level directly addresses the processing of information or learning processes requiring understanding or completing the task. In the third stage, feedback is focused on the self-regulation level, which gives confidence to a learner for further engaging on a task. An example of third-level feedback could be, “You already know the key symptoms of the Covid19. Check to see whether you have diagnosed them in your patients". The last level of feedback influence is more personal in that it is directed to the "self," which is often considered unrelated to performance on the task. An example of such feedback could be "That is an intelligent response, well done." In terms of the effectiveness of each feedback type, the study (Hattie et al., 2007) suggests that FS is the least effective. In contrast, FR and FP have a more powerful impact on task processing, and FT is mighty where the task information is used to improve performance.

FT (feedback about the task), the type of feedback used in this study, provides information as to whether the task performance is fulfilling, for instance, diagnosing clinical cases by choosing correct answers. FT is the most common feedback, also called corrective feedback, and it is associated with correctness, neatness, behavior, or some other criterion related to task accomplishment. Some meta-analyses studies address the reason behind the significant influence of FT (Lysakowski, 1981; Walberg, 1982; Goldring, 1989; reported an effect size of 1.13, 0.82, and 0.74, respectively). It is worth mentioning that FT is more effective for faulty interpretations, but not necessarily lack of information. Providing further instruction is more powerful than feedback information when students need necessary knowledge. On the other hand, providing too much feedback may even detract students from task performance (Kluger & DeNisi, 1996).

In a research done by Winne and Butler (1994), it was suggested that the advantage of FT depends on students' attention to the feedback information and students' memories of that information. It is argued that feedback at the task level could be more beneficial by providing information to reject erroneous data. Moreover, providing feedback about the task can give cues to guide students for searching information in a task or situation (Hattie et al., 2007; Harackiewicz, 1979; Harackiewicz et al., 1984). Feedback about the task can be presented with several dimensions, including the level of complexity, group vs. individual performance, and written vs.

numeric tasks. Some studies (Balzer, Doherty, & O'Connor, 1989) show that simple tasks influence more than challenging tasks.

In a study back in the 1980s (Kulhavy et al.), as an example, students were given reading passages with multiple-choice questions about the passages, followed by increasingly complex feedback. In the beginning, the correct answer was given to students, and then they discussed incorrect choices by reading the relevant part of the passage and explaining their reasonings. What Kulhavy saw was interesting, as providing less complex feedback resulted in better performance in subsequent tasks.

There are two ways of delivering feedback about the task (FT) in individual and group situations. Providing in groups can make the feedback perceived differently by each group member; therefore, it could be a good idea to present feedback individually. Another critical factor in giving feedback is the effectiveness of marks and written comments (Black & Wiliam, 1998; Crooks, 1988; Hattie, 2007). Much evidence supports the idea that providing written comments (specific FT) is more effective than giving grades. Some studies (Cardelle et al., 1981; Elawar et al., 1985; McLaughlin, 1974) show that short-written feedback rather than grades alone significantly improved task performance. A study by Butler (1987) suggested that grades could increase students' involvement; however, it does not improve performance. Moreover, feedback in the form of comments can lead to learning gains, whereas marks alone do not. Bulter's studies argued against the classroom culture of marks and grades and suggested focusing on personal improvement instead.

The effects of timing in feedback processing

Some studies (Kulik & Morgan, 1991; Schroth & Lund, 1993; Sturges, 1972; Hattie, 2007) suggest a significant effect of timing in feedback presentation, especially when contrasting immediate and delayed feedback. However, some of those researches do not consider the impact of different feedback types along with the effect of timing. In a study by Kulik (1988), they reported that having some delay in delivering feedback about a task (FT) could be beneficial, whereas, at the process level (FP), immediate feedback is more effective. The study also shows the effect of delayed feedback in learning experimental tasks where delayed feedback appeared to hinder learning.

Preservation-interference theory (Kulhavy & Anderson, 1977) is one of the theories that helps us understand the effect of timing on feedback processing. According to the theory, in the absence of delay in delivering feedback, some interference occurs between the memory of incorrect responses made during the acquisition phase and the memory of correct answers during the feedback phase. However, imposing some delay in delivering feedback separates the acquisition trial and feedback trial, giving incorrect responses time to fade, and new correct answers can be learned more efficiently during the feedback phase. In the immediate feedback condition, the trials are almost fused, and the memory structures interfere, but the two trials are separate by delaying feedback delivery. Therefore, delayed feedback appears to be more effective in learning than immediate feedback.

Positive and negative feedback

Both positive and negative feedbacks significantly affect learning and can have different effects at different feedback levels (Kluger & DeNisi, 1996). Hattie (2007) argues that negative feedback is more potent at the self-level (FS), whereas both positive and negative feedback can be effective at the FT level. At the self-level (FS), though, any praise followed by feedback about the task is more effective (Hattie et al., 2007; Brockner, 1979; Campbell, 1985).

In a study by Van-Dijk et al. (2001), the impact of positive feedback on increasing motivation was reported, whereas negative feedback decreased such motivation. The difference might be associated with the contribution level and how people like to be involved in the task. Therefore, at the self-regulation level, the tendency to achieve goals significantly impacts the effectiveness of positive and negative feedback. In other words, when we are committed to achieving something, we learn from positive feedback information; however, by doing a task we are not driven to, we might learn as a function of negative feedback. Receiving negative feedback makes students dissatisfied with their previous performance level and puts higher goals for future performance (Podsakoff et al., 1989). Nevertheless, as discussed earlier, positive feedback increases students' motivation to return to or persist in activity and set higher goals for the activity (Deci et al., 1999).

Regarding the effect of positive vs. negative feedback on FR, an interactive effect between positive and negative feedback has been suggested by Swann et al., 1988. The study showed that for students with a high level of self-efficacy, feedback about initial success (positive feedback) could highlight a talent, which later leads to better task performance since they take the positive feedback as a kind of verification of themselves.

It is worth mentioning that the level of self-efficacy in the negative feedback perception is also critical. For instance, students with high self-efficacy are more optimistic about their future performance after receiving negative feedback. In contrast, students with low self-efficacy can have a pessimistic prediction about their future task performance. Hence, negative feedback can impact subsequent motivation and performance for low self-efficacious students (Brockner et al., 1987). As in our case, where we provide feedback about the task, corrective information is a great tool to increase learning outcomes and skill proficiency. Therefore, giving negative feedback with disciplinary information is more effective than negative feedback without helpful/corrective information (Hattie et al., 2007; Weiner, 1977). It is also reported in the literature (Howie et al., 2000) that FT can even get ignored if it does not provide sufficient information or is poorly presented.

Other studies (Swann, 1985; Swann & Hill, 1982) show that students' attention to the feedback information is a key to task performance. In this process, students tend to focus on the feedback that fits their understanding of the self, and therefore they tend to arrange the environment to gain further self-confirming evidence. On the other hand, students tend to reject or ignore negative feedbacks on their behavior /performance that is different from their understanding (Hattie et al., 2007; Greenwald, 1980; Markus, 1977; Tesser & Campbell, 1983).

Models of feedback

As mentioned earlier, one of the primary purposes of providing feedback is to fill the gap between current performance and a standard. Feedback fills the gap by addressing the goals (What should be done?), progress towards achieving the goals (How is students' performance?), and activities required to make progress fast (What is the next step?), which are also referred to as feed-up, feedback, and feed-forward.

Among different methods of reducing the gap between the current and standard level of task performance, one is for students to increase effort. This method is more effective when dealing with particularly challenging tasks that require a higher level of experience. A good description of this method can be found in Kluger et al. (1996) study, where they quote, "we are more likely to increase effort when the intended goal is clear, when high commitment is secured for it, and when belief in eventual success is firm." Some studies (Hattie et al., 2007) suggest an alternative method to reduce the abovementioned gap: developing practical error detection skills.

Learning those skills could tremendously impact students' task performance, which can work as a self-regulatory mechanism where students develop a problem-solving mindset.

Teachers can also play a productive role in filling the gap between current and standard performance. Providing a clear understanding of goals is one of them. Clear and specified goals are influential in bridging the gap by focusing students' attention. However, general and unclear goals make it hard to achieve (Locke et al., 1984). Furthermore, teachers' feedback can make students more committed to achieving the goal and increase students' efforts towards goals.

Overview of magnetic resonance imaging (MRI)

In this section, we go through a general overview of the main concepts of magnetic resonance imaging. The first concept to know is nuclear magnetic resonance, introduced by an experiment designed by Nobel prize laureates Bloch and Purcell in 1946 (Bloch et al., 1946; Purcell et al., 1946; Grover et al., 2015). The concept of NMR alongside superconducting technology brought a new method in medical imaging. For the first time, scientists in Aberdeen (1980) could successfully produce an image using the magnetic resonance imaging technique, and now it is over 30 years that humans and animals are both enjoying the non-invasive procedure of MR imaging (Hawkes et al., 1980; Grover et al., 2015).

Based on the atomic model, a nucleus consists of protons and neutrons. One of the critical properties of a nucleus is spin which directly depends on the number of protons. The concept can be thought of as the spinning of a nucleus on its axis. To be more precise, it is not the nucleus that spins around its own axis; it is the magnetic moment of a nucleus that does spin and consequently generates a magnetic field. (Westbrook, 2011; Grover et al., 2015)

Hydrogen is a crucial component in magnetic resonance imaging (MRI) because it is the most abundant element in the human body, and it has a strong magnetic moment. MRI works by aligning the hydrogen atoms in the body with a strong magnetic field and then applying a radiofrequency pulse to the body, which causes the hydrogen atoms to absorb and emit energy. Exposing those spinning hydrogen nuclei that have produced magnetic moments to an external magnetic field (B0), which is by far more substantial than the magnetic moment of a hydrogen nucleus, aligns the nucleus either in parallel with or perpendicular to the external field. As a result, by placing a specimen containing many nuclear spins inside the B0 field, spins will go into two energy states, a lower energy state parallel to B0 and a higher energy state perpendicular to B0. The angular momentum of the nucleus due to its rotation will also rotate around the axis of B0. The velocity of rotation around the B0 axis is called the Larmor frequency, which is proportional to the field strength and is described by the Larmor equation (Westbrook, 2011; Grover et al., 2015):

$$\omega_0 = {}_{\gamma}B_0$$

In order to excite a spinning nucleus inside the huge external magnet B0, we need to apply another magnetic field perpendicular to the main B0. This secondary magnetic field is generated in short pulses (at the scale of a millisecond), and more importantly, the frequency of these pulses should be close to the Larmor frequency of target nuclei. RF pulses are used to manipulate the hydrogen atoms in the body by altering their spin orientation. These pulses are typically applied perpendicular to the direction of the main magnetic field B0. When an RF pulse is applied, the hydrogen atoms absorb energy and then release it as a signal. The frequency and duration of the RF pulse can be adjusted to target specific types of tissue or to create different types of contrast in the resulting image. Therefore, by applying smaller but near Larmor frequency RF pulses, the phenomenon of magnetic resonance occurs, and nuclei get into the excitation state where they transition from lower energy level to higher and vice versa. As a result of nuclei excitation, they gain energy and later release that absorber energy to the surrounding molecular lattice, which can be easily measured using a detector. The process of releasing thermal energy by excited nuclei into the surrounding lattice is called the relaxation process and is considered one of the image contrasts in MR imaging (Westbrook, 2011). This relaxation process consists of two components: T1 recovery and T2 decay. When the RF pulse is turned off, the hydrogen atoms return to their original state and realign with the longitudinal axis, or Z-axis, with a time constant called T1. In contrast, the hydrogen atoms on the transverse plane, or X-Y axes, release magnetization through spin-spin decay with a time constant of T2. By utilizing T1 and T2 as a contrast, various types of images, including structural and functional images, can be generated in MRI research. It should be noted that the effect of magnetic inhomogeneity impacts the T2 decay time and makes it decay faster. This effect is demonstrated by $T2^*$.

The energy released in relaxation, also known as Free Induction Decay (FID), is relative to the energy difference between two nuclear spin states. This energy depends on the main magnetic field of B0. For the purpose of signal-to-noise (SNR) enhancement, multiple Rf pulses are applied, and the average of the recorded signals gives a better measure of the FID signal. The output FID signal comprises information from all nuclei in the selected field of view (FOV).

To locate signals produced by hydrogen atoms gradients are used. Gradients are small magnets that are used to create a magnetic field that varies in strength along different directions within the body. The gradient field causes the hydrogen atoms in different regions of the body to precess at slightly different frequencies, allowing the MRI machine to distinguish between signals from different parts of the body. The spatial encoding provided by gradients enables the creation of 2D or 3D images of the internal structures of the body.

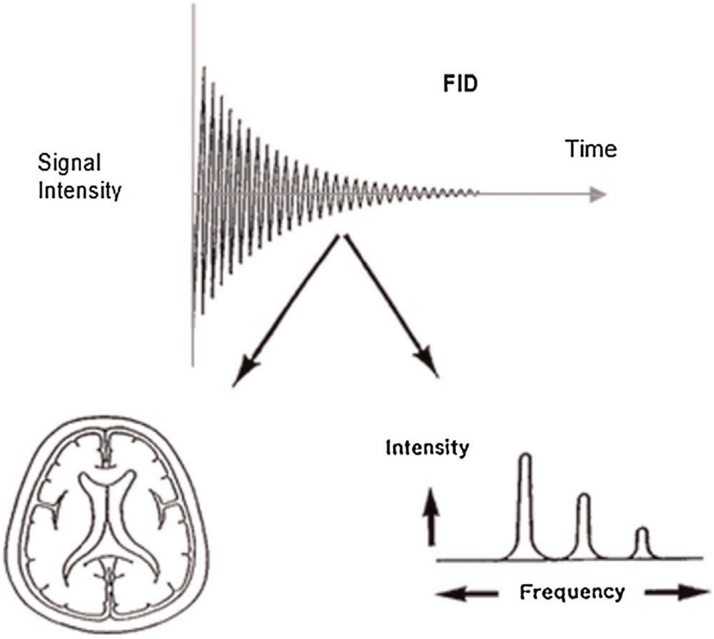

Figure 1 The free induction decay (FID) and Fourier transformation to generate MR images or MR spectra. (Westbrook, 2011; Grover et al., 2015)

Functional magnetic resonance imaging (fMRI) is one of the famous MRI techniques which allows us to study neural activity over time by recording the hemodynamic response of neural regions (Huettel et al., 2009). The hemodynamic mechanism of neural activity can be thought of as an increase in blood flow following a neuronal activity, which results in signal change termed blood oxygen level-dependent (BOLD). The BOLD signal represents the ratio of oxyhemoglobin versus deoxyhemoglobin within the neuroactive region. Using different physical properties of oxyhemoglobin and deoxyhemoglobin inside the magnetic field (B0), we can record the oxygenation level of brain regions indicative of neuronal activity.

By taking advantage of the distinct physical properties of oxyhemoglobin and deoxyhemoglobin in the presence of a magnetic field (B0), it is possible to measure the oxygenation levels of specific brain regions, which can provide valuable insights into neuronal activity. This technique, known as functional magnetic resonance imaging (fMRI), relies on the fact that deoxyhemoglobin is paramagnetic and disrupts the local magnetic field, leading to a decrease in the MRI signal, while oxyhemoglobin is diamagnetic and has little effect on the magnetic field. As a result, changes in blood oxygenation levels can be detected by measuring the changes in the MRI signal over time, allowing for the visualization of brain regions that are activated during specific tasks or stimuli.

There are two main experimental paradigms in fMRI studies, block design and event-related. In so-called block designs, stimuli are presented to participants in alternating short runs, experimental blocks, and rest blocks. After that, MRI signals of those blocks, experimental vs. rest blocks, are compared against each other to identify the neuronal activity of experimental blocks. In a block design paradigm, those voxels unaffected by the stimulation should result in a steady set of data points, with some fluctuation due to physiological changes that are not necessarily related to the brain state. (Gore et al., 2003)

The second experiment design type, an event-related paradigm, uses transient stimuli. This paradigm applies to other neuroimaging techniques, including event-related potentials (ERPs) in electrophysiological studies. This method is widely applicable because of its effectiveness in identifying different cognitive functions by providing different experimental designs. Therefore, a BOLD response can be elicited by presenting a set of stimuli, and then the average response of multiple epochs indicates fMRI signal change.

Hypothesis

In our study on feedback processing in clinical decision-making, we hypothesized that brain regions such as the Prefrontal cortex (PFC), Dorsolateral PFC (DLPFC), Ventromedial PFC (VMPFC), Cingulate cortex (especially the anterior cingulate cortex ACC), and striatum would be activated when participants received feedback. These regions have been previously shown to be involved in decision-making and reward-related behaviors, as reported by Becker et al. (2014) and Holroyd et al. (2005). We also predicted that presenting positive feedback would evoke stronger activation in these regions compared to negative feedback. Additionally, we aimed to compare the neural activation patterns in response to feedback between easy and hard cases. Based on our hypothesis, we expected to observe increased activation in brain regions associated with analytic processing during the hard case condition.

Chapter 2: Methods

Study design

In this study, we use a block design paradigm in which experimental blocks of feedback processing are compared to rest blocks called fixation periods. The fixation periods can be considered baselines where no stimuli are presented (Hruska et al., 2015; Raichel et al., 2006). The average of neural activity during feedback blocks versus fixation blocks is the signal contrast indicating neural activity of the feedback processing phase. If the average activation during feedback blocks is more remarkable than fixation blocks, the neural activity is thought to be associated with the cognitive process of clinical feedback processing. This signal extraction method is termed cognitive subtraction, where the contrast of different brain states is investigated to see if they differ in only one discrete feature (the independent variable). In cognitive subtraction, the general assumption is "pure insertion," which suggests inserting one single cognitive process into a task/stimulus without disrupting the remaining processes. In other words, it indicates that there are no interactions among the cognitive components of a task (Harrison et al., 2010).

The block design of this study consists of clinical cases with multiple-choice questions, which were presented in a timely manner, called "run." Generally speaking, a run is a period of time where one single task is given to a participant without interruption. As for our task design, each run was 180 seconds long, and all runs were randomly presented. Figure 2 shows a timeline of one run, including reading a clinical case, answering a multiple-choice question, expressing confidence, and finally displaying feedback. Of note, the feedback processing phase is the main focus of the current study.

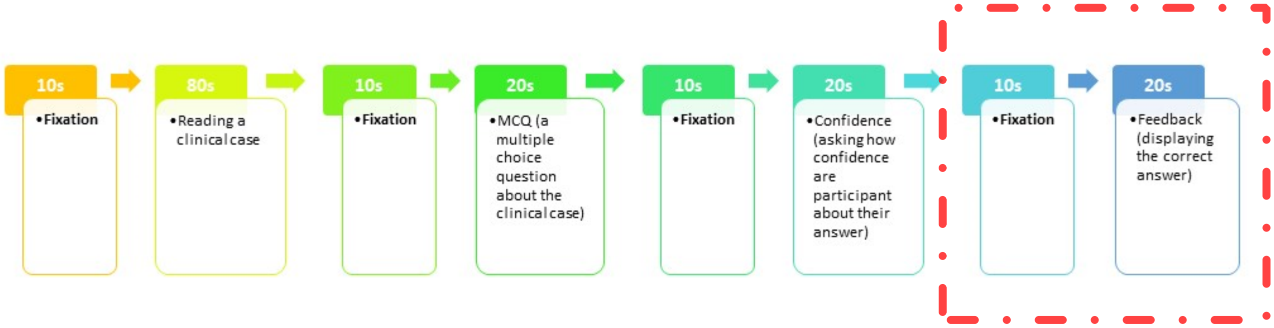

Figure 2 Timing diagram of a run (red box shows the feedback processing and the fixation phase investigated in this study)

Subjects and sample size

In this study, we investigated 24 subjects, 12 novices (second-year medical students) and 12 expert clinicians (fully certified gastroenterologists), to study neural regions involved in the feedback processing of clinical decision-making. More specifically, our goal was to investigate if there are any different neurocognitive effects of clinical expertise (experts vs. novices) and clinical case difficulty (hard vs. easy) in feedback processing of clinical decision-making. Therefore, the quantitative and statistical investigation of those effects is not in the scope of this study, and our findings only address if neural areas of activation for our study groups/contrasts are different. It is worth mentioning that the sample size used in this study is considered a typical sample size in fMRI experiments. (Hruska et al., 2015; Huettel et al., 2009; Guo et al., 2012)

From a data analysis point of view, though, to find out whether neural areas of activation are associated with a task/contrast (novice vs. expert participant, easy vs. hard question, positive vs. negative FB) fixed effect analysis could be a helpful analysis method (Friston et al., 1999). We used this method in our group analysis.

fMRI data collection and analysis

The imaging and data collection was performed at the University of Calgary, SFMR Centre at Foothills Medical Centre, Calgary, AB, on a 3T GE MRI scanner MR750 (Hruska et al., 2015). The imaging study began with a high-resolution T1 structural image using a Spin-echo sequence with voxel dimensions of 1x1x1mm. This was followed by functional imaging using GRE-EPI sequences, with the same voxel size and orientation as the T1 image. The functional imaging was performed on the axial plane, with a bottom-up and interleaved slice acquisition. The imaging parameters included a TR of 2s, TE of 20ms, FA of 70 degrees, 37 slices, each with a thickness of 3mm in a volume, and a field of view (FOV) of 24cm with a resolution of 64x64 pixels. A 16-channel phased array receiver coil was used for data collection. Each functional run lasted for 180s and contained 90 volumes of EPI data.

In order to prepare fMRI data for higher-level analysis, some preliminary analysis steps, called pre-processing, should be applied to the data. The pre-processing steps include quality assessment (raw data assessment for excluding data with visually detectable artifacts), brain extraction using BET (removing non-brain tissues), co-registration (registering EPI to T1 data for each subject), slice timing correction (registering all slices of a volume to a reference slice), motion artifact correction, normalization (registering T1 data to a standard brain, MNI 152), and spatial smoothing (for SNR enhancement purposes, with Gaussian kernel of 5.0 mm FWHM). All data were pre-processed successfully using the FSL software package - version 6.0, FMRIB analysis group, Oxford University, UK. However, quality assessment requirements excluded some runs from data analysis.

In GLM (general linear model) design of this study, we had three levels of data analysis, starting from the first level, voxel-wise analysis, where the activation pattern of a voxel was analyzed to determine its correlation with the task pattern. As we have consistent task design for all runs, time points of task sequences are fixed, and specifically, the onset of the feedback task was used to perform data analysis relative to the time point of interest. As shown in figure 2, we have five-time points in each run, and our focus time point in this study is the feedback phase which starts from the 160th second to the end of the run.

Table 1 shows the timeline of the task and the onset of contrast parameters. As mentioned earlier, the main focus of this study is to investigate the effect of feedback in clinical decision-making; hence, the main contrast/parameter of interest is the feedback phase highlighted in the table. The analysis results at this level are the mean activation of brain regions associated with feedback (our contrast of interest) for each participant. Figure 3 has the same information as table 1 and simplifies the timing diagram of a run. Red boxes in both table 1 and figure 3 show the feedback processing phase of this study.

Table 1 First-level parameters of interest and onset times

Contrast of interest	Fixation 1	Reading	Fixation 2	MCQ	Fixation 3	Confidence	Fixation 4	Feedback
Onset (s)	0	10	90	100	120	130	150	160
Duration (s)	10	80	10	20	10	20	10	20

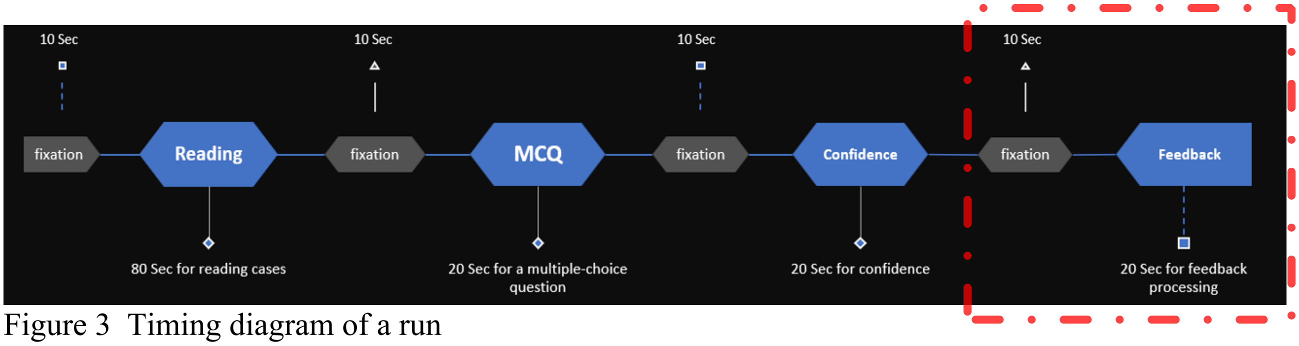

Figure 3 Timing diagram of a run

The second-level group analysis (hard vs. easy questions and positive vs. negative feedback) is performed following the first-level analysis. At this level, each subject's activation was taken into a group analysis to investigate the effect of easy vs. hard questions and positive vs. negative feedback. Therefore, in this stage of group analysis, we have eight contrasts, as shown in Table 2.

In the third-level analysis, the output of the second-level analysis is used for group analysis purposes, where novice participants are compared to experts. The second column of table 2 represents the contrast used in the third-level analysis.

Table 2 Contrasts in second-level group analysis

Contrasts of second-level analysis	Contrasts of third-level analysis
Easy	
Hard	
Positive FB (correct Ans)	Novice
Negative FB (incorrect Ans)	Expert
Easy > Hard	Novice > Expert
Hard > Easy	Expert > Novice
Positive > Negative	
Negative > Positive	

Following performing statistical analyses on neuroimaging data, it is common to conduct multiple statistical tests to prevent the increase of the likelihood of false positives. Therefore, it is important to control the family-wise error rate (FWER) or false discovery rate (FDR) to reduce the probability of type-I errors. In FSL, there are several ways to control the FWER or FDR. One approach is to use cluster-based thresholding, which groups nearby significant voxels into clusters and applies a threshold based on the size of the cluster. In our study we used cluster-based thresholding (Z-value of 2.3 and p-value of 0.05) for multiple comparison purposes.

The brain atlas is one of the essential tools in fMRI data analysis. Generally speaking, an atlas is a standard set of coordinates that allows one to locate a specific brain region. Several brain atlases are used in the FSL software package, and in this study, Harvard-Oxford Cortical/subcortical Structural Atlas is used for different registration purposes. One of the main parameters in fMRI data analysis is cluster threshold, which determines a cluster's activation level. A cluster is defined as a set of neighboring voxels in a brain region that could be functionally connected. In this study, a statistical threshold of $Z=2.3$ (Z score) and $p < 0.05$ (P value) is used as an indicator for cluster-wise activation. After performing data analysis based on cluster-wise activation, an ROI analysis was also performed to double-check the activation of some essential brain regions (OFC, PFC, ACC) that we hypothesized to be involved with feedback processing.

The data collection procedure followed some MRI safety guidelines (Hruska et al., 2015). One of the primary safety considerations is ensuring participants do not have magnet-sensitive devices, including metal body implants. On the other hand, the loud noise of the MRI machine itself is dangerous for unprotected ears and can also have a distractive impact on participants' cognitive performance. Therefore, some MR-compatible ear protection devices (earplugs and headphones) were used during data acquisition. Participants were also provided a questionnaire about their mental health and medication consumption. This measure ensured that participants in this study had healthy normal brains and hemodynamic responses (BOLD signals) and were not affected by substances and medications.

It is clear, though, despite all these efforts, inside the MRI machine is not an ideal environment for cognitive tasks, and there is a number of noises and artifacts involved in the MRI studies. Nevertheless, this is the best non-invasive neuroimaging tool at present.

Chapter 3: Manuscript one- Neural areas of activation during feedback processing in clinical decision making.

Abstract

Studies in neural areas of activation during clinical reasoning and decision-making play a critical role in improving medical education; however, the effect of feedback processing in clinical decision-making is poorly understood. In particular, differences in feedback processing in novice and expert clinicians during clinical decision-making. To understand these differences, we presented feedback (correct/incorrect diagnosis) to novice and expert clinicians after diagnosing simple or complex (easy, hard) cases while functional magnetic resonance imaging (fMRI) data were collected. Using a block design paradigm, we compared experimental blocks of feedback processing with rest blocks called fixation periods. Sixteen clinical cases (in the field of gastroenterology) were presented in the form of multiple-choice questions during an fMRI scanning session. The length of each clinical case was about 220 words, and they were shown using a projection system provided by Avotec Company. Feedback was presented to the participants at the last 20 seconds of the imaging trial after 10 seconds of the fixation period. To investigate neural activities of feedback processing, we contrasted the average signal of neural activity in feedback blocks against the average signal of neural activity in fixation blocks. A greater activation level of feedback blocks can be associated with the cognitive load of feedback processing.

fMRI was used to scan twelve second-year medical students and twelve practicing gastroenterologists while they were provided feedback (correct/incorrect diagnosis) during a one-hour scanning session. Giving feedback for clinical diagnosis evoked multiple neural activations in some cortical regions like the cingulate cortex, temporal gyrus, Caudate, Orbitofrontal cortex,

and occipital cortexes in novice and expert groups. A significant increase in activation of those areas in the novice group for both positive and negative feedback suggests novice group utilizes WM, motivation, and reward more than the experts. Further investigation within each group showed considerably more activation in temporal and cingulate cortexes and Caudate for positive feedback than negative feedback in both participant groups.

This study suggests a relationship between feedback processing, working memory, motivation, and reward processing. More specifically, the level of expertise and the type of feedback elicited differential activation in the temporal cortex, cingulate cortex, and Caudate. These activations could be associated with WM, learning, motivation, and reward processing.

Introduction

Accuracy in clinical decision-making and diagnosis plays an essential role in patient care; therefore, medical decision-making skills are crucial for a successful diagnosis. On the other hand, as a significant part of the learning process, feedback aims to narrow the gap between observed and standard performance by providing the learner with information to assess their performance. The gap could be filled by restructuring the learned structures, providing guiding information to students, and introducing new methods to understand particular concepts. In a review study by Winne and Butler (1994), it is suggested that feedback can be defined as the information which helps a learner to confirm, add to, overwrite, tune, or restructure memory information.

Research in medical education has aimed to discover the neurocognitive processes of clinical decision-making, done mainly by indirect and non-invasive methods, to investigate the effect of experience level, medical education, and feedback in learning. There are different types of tasks in the literature for studying medical decision-making. Some are visuospatial/ diagnostic imaging tasks (Melo et al., 2011; Bahrami et al., 2014), tasks that explore the brain regions involved with decision-making in different cognitive states (Durning et al., 2014), and tasks that target the analytic and non-analytic decision making. In this study, we focus on feedback processing in clinical decision-making and how this cognitive process is affected by the type of feedback (positive vs. negative feedback), level of clinical expertise (novice and expert clinicians), and clinical case difficulty (hard and easy cases).

Feedback in clinical decision making.

There are some studies (Hattie et al., 2016) suggesting four levels for the influences of feedback processing, including feedback about the task (FT), processing of the task (FP), self-regulation (FR), and a person himself (FS).

First, feedback can be about a task, as to whether a doctor's diagnosis is correct or incorrect. The second level of feedback aims at the process of completing a task. This level directly addresses the processing of information for completing the task. In the third stage, feedback is focused on self-regulation, which gives confidence to a learner for further engaging on a task. An example of third-level feedback could be, "You already know the key symptoms of the Covid19. Check to see whether you have diagnosed them in your patients". The last level of feedback influence is more personal in that it is directed to the "self," which is often considered unrelated to performance. An example of such feedback could be, "That is an intelligent response; well done."

The study (Hattie et al., 2007) also suggests that FS is the least effective feedback. In contrast, FR and FP are more potent in influencing task processing, and FT is powerful, where the task information is used to improve task performance.

FT (feedback about the task), the type of feedback used in our study, provide information as to whether the task performance is fulfilling, for instance, diagnosing clinical cases by choosing correct answers. FT is the most common feedback, also called corrective feedback or knowledge of results. It is associated with correctness, neatness, behavior, and other criterion related to task accomplishment. The reason behind the strong influence of FT is addressed by various meta-analyses studies (Lysakowski, 1981; Walberg, 1982; Goldring, 1989 reported an effect size of 1.13, 0.82, and 0.74, respectively). It is worth mentioning that FT is more effective for faulty interpretations, but not necessarily lack of information. Providing further instruction is more powerful than feedback information when students need necessary knowledge. On the other hand, providing too much feedback within a level may even detract students from task performance. (Kluger & DeNisi, 1996).

Some studies (Kulik & Morgan, 1991; Schroth & Lund, 1993; Sturges, 1972; Hattie, 2007) suggest a significant effect of timing in feedback presentation, especially when contrasting immediate and delayed feedback. However, some of those researches do not consider the impact of different feedback types along with the effect of timing. In a study by Kulik (1988), it is reported that having some delay in delivering feedback about a task (FT) could be beneficial, whereas, at the process level (FP), immediate feedback is more effective. The study also shows the effect of delayed feedback in learning experimental tasks where delayed feedback appeared to hinder learning.

Preservation-interference theory (Kulhavy & Anderson, 1977) is one of the theories that helps us understand the effect of timing on feedback processing. According to the theory, in the absence of delay in delivering feedback, some interference between the memory of incorrect responses made during the acquisition phase and the memory of correct answers during the feedback phase occurs. However, imposing some delay in delivering feedback separates the acquisition trial and feedback trial, giving incorrect responses time to fade, and new correct answers can be learned more efficiently during the feedback phase. In the immediate feedback condition, the trials are almost fused, and the memory structures interfere, but the two trials are separate by delaying feedback delivery. Therefore, delayed feedback appears to be more effective in learning than immediate feedback.

The feedback type is a critical factor that significantly impacts learning (Kluger & DeNisi, 1996). Hattie et al. (2007) suggest that the kind of feedback (FT, FP, FR, FS) plays a more critical role than positive vs. negative feedback. Moreover, he argues for negative feedback to be more potent at the self-level (FS), and both types can be effective as FT; however, there are some differences regarding task performance. At the self-level (FS), though, any praise followed by feedback about the task is effective. Negative feedback at the self-level (disconfirmation) can be more potent than positive feedback. (Hattie et al., 2007; Brockner, 1979; Campbell, 1985). Regarding positive vs. negative feedback on FR, an interactive effect has been suggested between positive and negative feedback (Swann et al., 1988). They showed that for students with a high level of self-efficacy, feedback about initial success (positive feedback) could highlight a talent, which leads to better task performance.

As in our case, where we provide feedback about the task, corrective feedback is a great tool to increase learning outcomes and skill proficiency. Therefore, giving negative feedback with corrective information is more effective than negative feedback providing no helpful/corrective information (Hattie et al., 2007; Weiner, 1977). It is also reported in the literature (Howie et al., 2000) that FT can even get ignored if it does not provide sufficient information or is poorly presented.

fMRI studies in medical education

Several neuroimaging studies in the literature address brain regions involved in decision-making in clinical setups (Hruska et al., 2015; Durning et al., 2014; Downar et al., 2011). The results from those studies suggest that neural activation in the prefrontal cortex (PFC) is associated with analytical reasoning (AKA type 2 decision-making). On the other hand, investigating clinical decision-making through non-analytic reasoning (AKA type 1 decision-making) shows common brain regions among participants with different levels of expertise. Interestingly, activation of PFC among expert physicians is reported to be smaller than that of inexperienced ones.

Functional connectivity among those active regions is also reported to vary due to the effect of medical education. Sheena (2018) reports a significant difference in functional connectivity between medical interns (med students with four and haft years of schooling) and first-year medical students. The study shows differences in resting state fMRI of the right inferior temporal gyrus, right supplementary motor cortex, and left cerebellum. There are also some studies about reward processing and feedback-related negativity (FRN) reporting some of the brain regions during those cognitive tasks (Becker et al., 2014; Holroyd et al., 2004; Cohen et al., 2004; Nieuwenhuis et al., 2005).

Purpose

The primary purpose of this study was to investigate the differences between novices and experts during feedback processing of clinical decision-making, focusing on the role of feedback types (positive vs. negative feedback) and clinical case difficulty (hard vs. easy case).

Hypothesis

Regarding neural areas involved in feedback processing in clinical decision-making, our primary hypothesis was to see some common neural regions associated with reward processing, learning, and memory. Neural areas such as the Prefrontal cortex (PFC), Dorsolateral PFC (DLPFC), Ventromedial PFC (VMPFC), Cingulate cortex (specifically anterior cingulate cortex

ACC), and striatum have been reported to play active roles in decision-making and reward-related behaviors (Becker et al., 2014; Holroyd et al., 2005) and we hypotheses that these brain regions could be evoked by presenting feedback to participants of this study.

Methods

Participants

In this study, we investigated 24 subjects, 12 novices (second-year medical students) and 12 expert clinicians (fully certified gastroenterologists), to study neural regions involved in the feedback processing of clinical decision-making. More specifically, our goal was to investigate if there are any different neurocognitive effects of clinical expertise (experts vs. novices) and clinical case difficulty (hard vs. easy) in feedback processing of clinical decision-making. Our novice participants (4 females and 8 males, ranging from 22 to 38 years old) were all medical students at Cumming school of medicine at the University of Calgary, and they had completed a gastrointestinal course one year before volunteering in our study. The second group of participants in this study were practicing gastroenterologists (7 female, 5 male, ranging from 32 to 50 years old). All participants were right-handed, with normal vision, and had no medical (neurovascular or neurophysiological abnormality) history. The data collection of this study was conducted by Dr. Kent's lab at the University of Calgary (Hruska et al., 2015). All procedures are under the ethical standards outlined by the Calgary Health Ethics Research Board (CHREB) and the Seaman Family MR Research Center at Foothills Medical Centre, Calgary, AB, Canada.

Tasks and procedures

Each run consists of 3 minutes of fMRI data collection for reading, answering, and feedback processing of one gastroenterology clinical case. The length of each clinical case was about 220 words, and they were shown using a projection system provided by Avotec Company. For every participant, 16 runs were randomly presented in a one-hour fMRI scanning session using Presentation® (Version 16, www.neurobs.com). Feedback was given to the participants at the last 20 seconds of the imaging trial after 10 seconds of the fixation period. Figure 3 represents the timing diagram of a run.

Among clinical cases, there are eight easy cases and eight hard ones. Easy cases are those with analytic data supporting clinical case description, whereas, in hard cases, the analytic data do not necessarily support case description and are discordant with it. As mentioned earlier, the general topic of clinical cases is gastroenterology, and the subtopics are elevated liver enzymes, diarrhea, dysphagia, and anemia. We had four questions in each subtopic.

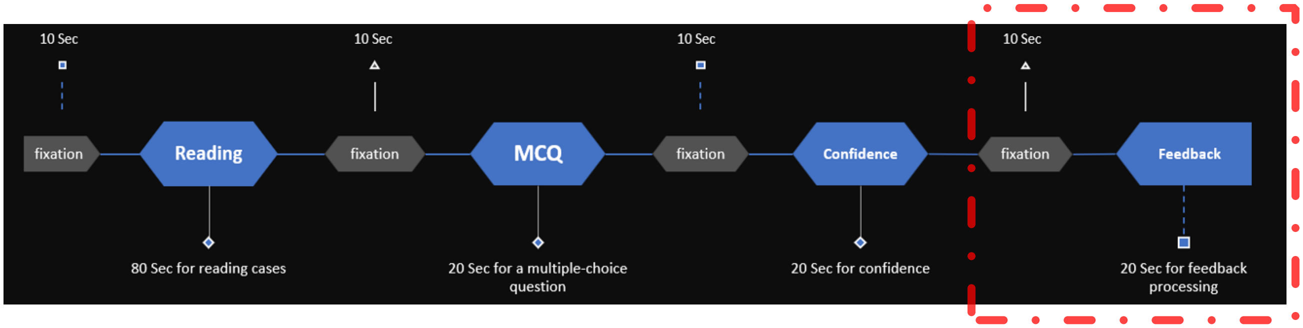

Figure 4 Timing diagram of a run

fMRI data acquisition and analysis

The imaging and data collection was performed at the University of Calgary, SFMR Centre at Foothills Medical Centre, Calgary, AB, on a 3T GE MRI scanner MR750 (Hruska et al., 2015). The imaging trials were begun with a structural T1 image using a Spin-echo sequence (high-resolution 1×1×1mm), followed by functional imaging using GRE-EPI sequences. Voxel size and orientation of both T1 structural and T2 functional images were the same. Some imaging parameters are as follows: functional imaging on axial plane, bottom-up and interleaved slice acquisition, TR=2s, TE=20ms, FA=70’, volume size 111mm thickness (37 slices, 3mm each), FOV=24cm with 64×64 pixels resolution. The data collection coil was a 16-channel phased array receiver coil. Each functional run was 180s long, containing 90 volumes of EPI data.

In order to prepare fMRI data for higher-level analysis, some preliminary analysis steps, called pre-processing, are needed to be applied to the data. That pre-processing includes quality assessment (raw data assessment for excluding data with visually detectable artifacts), brain extraction using BET (removing non-brain tissues), co-registration (registering EPI to T1 data for each subject), slice timing correction (registering all slices of a volume to a reference slice), motion artifact correction, normalization (registering T1 data to a standard brain, MNI 152), spatial smoothing (for SNR enhancement purposes, with Gaussian kernel of 5.0 mm FWHM). All data were pre-processed successfully using the FSL software package - version 6.0, FMRIB analysis group, Oxford University, UK. However, some runs were excluded from data analysis that did not meet quality assessment requirements. In the GLM design of this study, we considered three levels of data analysis, starting from the first level, voxel-wise analysis, where the activation pattern of the voxel was analyzed to determine its correlation with the task pattern. The outcome of this level of analysis is a time series representing the activation of a voxel, which was later convolved using a gamma function and contrasted with rest state data (10 seconds of fixation data). In the second level of data analysis, the parameter estimate map, as well as the variance map from the first level of data analysis, were grouped into easy (8) and hard (8) average images as well as positive and negative feedback (correct vs. incorrect answers) for contrasting purpose. Finally, we grouped the results of the second-level analysis into two groups of participants (experienced and novice clinicians) to contrast group effects (table 2 shows the contrasts in group analysis). From a data analysis point of view, to find out whether neural areas of activation are associated with task design (novice vs. expert participant, easy vs. hard question, positive vs. negative FB), fixed effect analysis could be a helpful analysis method (Friston et al., 1999) and this method was used in our group analysis.

Table 3 Contrasts in second-level group analysis.

Contrasts of second-level analysis	Contrasts of third-level analysis
Easy	
Hard	
Positive FB (correct Ans)	Novice
Negative FB (incorrect Ans)	Expert
Easy > Hard	Novice > Expert
Hard > Easy	Expert > Novice
Positive > Negative	
Negative > Positive	

One of the main parameters in fMRI data analysis is cluster threshold, which is used to determine a cluster's activation level. A cluster is defined as a set of neighboring voxels in a brain region that could be functionally connected. In this study, a statistical threshold of $Z=2.3$ (Z score) and $p < 0.05$ (P value) is used as an indicator for cluster-wise activation. Following the primary data analysis based on cluster-wise activation, an additional ROI analysis was conducted to validate the activation of specific brain regions that we hypothesized to be involved in feedback processing, such as the Orbitofrontal cortex (OFC), Prefrontal cortex (PFC), and Cingulate cortex.

The statistical criteria for p-value and z-value remained consistent with the previous analysis. The ROI analysis confirmed the activation of the predicted regions of OFC, PFC, and ACC for both participant groups and both types of feedback. These findings provide additional support for the involvement of these regions in feedback processing during clinical decision-making.

Following performing statistical analyses on neuroimaging data, it is common to conduct multiple statistical tests to prevent the increase of the likelihood of false positives. Therefore, it is important to control the family-wise error rate (FWER) or false discovery rate (FDR) to reduce the probability of type-I errors. In FSL, there are several ways to control the FWER or FDR. One approach is to use cluster-based thresholding, which groups nearby significant voxels into clusters and applies a threshold based on the size of the cluster. In our study we used cluster-based thresholding (Z-value of 2.3 and p-value of 0.05) for multiple comparison purposes.

Results

Our analyses aimed to address the group activation contrast for the novice and expert clinicians while they were provided with feedback for their clinical diagnoses to investigate the brain regions involved in differential activation for positive vs. negative feedback, novice vs. expert clinicians, and hard vs. easy clinical cases. The results show that different types of feedback significantly change hemodynamic activity in multiple brain regions for novice and expert clinicians, Figure 4-9; Tables 4, 5 (see supplemental tables for full details). Providing feedback, either positive or negative, is found to be associated with neural activations in some cortical regions, including the cingulate cortex (ACC and MCC), temporal lobe, Striatal structures (caudate and putamen), Orbitofrontal cortex (VMPFC), and occipital lobe in both novice and expert groups. In other words, those brain regions are common neural areas of activation for both groups, for both FB types, and for both hard and easy questions. However, the novice group had a more extensive cluster size of activation, as shown in the cluster size column of tables 4 and 5. This finding could suggest that the novice group was more involved with motivation, reward processing, language processing, and working memory than the experts. Looking at group differences indicates that the right caudate nucleus was significantly active for positive feedback, whereas negative feedback slightly activated the left caudate nucleus in both groups. Furthermore, the left cingulate cortex showed greater activation in the novice group, whereas the right cingulate cortex showed activation in experts. (Figures 7 and 8, and tables in Appendix B)

The behavioral results of our study indicate that clinicians expertise and clinical case difficulty have significant impacts on accuracy and response time in clinical decision-making. Specifically, the results demonstrate that experts outperform novices in both accuracy and speed of diagnosis, as they correctly diagnosed more cases and did so faster. Moreover, the analysis shows that participants overall were more accurate on easy cases compared to hard cases, and they also answered easy cases more quickly than hard ones. Interestingly, there were no significant interaction effects observed between expertise and case difficulty in both accuracy and response time analyses, suggesting that the impact of case difficulty was consistent across both groups of participants. These results provide valuable insights into the factors that affect clinical decision-making and suggest that experience and case difficulty are important factors to consider when assessing diagnostic performance.

Discussion

The primary purpose of this study was to investigate the differences between novices and experts during feedback processing of clinical decision-making, focusing on the role of feedback types (positive vs. negative feedback) and clinical case difficulty (hard vs. easy case). Our findings suggest a commonality between neural areas of activation in both groups of participants, including the right middle and superior temporal cortexes, left middle occipital cortex, and left middle orbitofrontal cortex. Despite those commonalities, however, the novice group had a more extensive activation cluster size in those common areas (Figure 4 - 9). Positive feedback evoked the right caudate nucleus, while negative feedback slightly activated the left caudate nucleus in both groups. There was greater activation in the left cingulate cortex for positive feedback in the expert group relative to novices. The left middle orbitofrontal cortex was significantly active for positive and negative feedback in both groups.

Common striatal activations found in this study are consistent with areas identified in studies related to reward during decision-making (Satterthwaite et al., 2007; McClure et al., 2003). Several neuroimaging studies have reported striatal responses to positive feedback in humans (Delgado et al., 2003; Knutson et al., 2001).

More specifically, ACC and MCC activations for positive feedback found in this study are consistent with the study published by Becker (2014), which reported feedback-related BOLD-responses in the striatum to positive but not negative feedback. In another study by Holroyd (Holroyd et al., 2005), several brain areas, including the rostral anterior cingulate cortex, posterior cingulate cortex, right superior frontal gyrus, and striatum were activated more strongly by positive feedback than by negative feedback, also reported.

Our neuroimaging results also showed a considerable activation of the left orbitofrontal cortex in feedback processing (both positive and negative) for both groups. This finding is consistent with recent studies (Kringelbach, 2005) that suggest the role of the orbitofrontal cortex in learning, decision-making, and reward-related behaviors. Further studies (Hornak et al., 2004; Rolls, 2004) have also confirmed the role of the orbitofrontal cortex (e.g., VMPFC) in learning and reward processing.

As for the effect of case difficulty on feedback processing in clinical decision-making, novice clinicians showed significant activation in the number of brain regions (as shown in table 11, 13) than experts. Lateralization of those areas is also consistent with the level of case difficulty; activation of brain regions in feedback processing of hard cases is more in the left hemisphere and for easy cases in the right hemisphere. Some brain areas are active for experts more than novices (tables 10 and 12, figure 8).

These results reveal brain regions involved with feedback processing in the clinical field by looking at the effect of different contrasts (level of expertise, type of feedback, and case difficulty), which suggests that feedback is associated with learning, reward processing, and memory. Differences in activation regions between the two groups highlight that the novice group demands more working memory, motivation, and reward processing. Significant activation of OFC shed light on the critical role of feedback in learning and decision-making.

Table 4 Areas of neural activation for positive and negative feedback on expert participants

Positive feedback processing (corresponds to the blue color in the top row of Fig. 3.1)

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
Right	Calcarine	13916	6.31	12	84	17
Right	Middle temporal gyrus	13476	5.5	43	70	13
Right	Caudate	7406	5.6	4	11	6
Right	Insula	4047	5.6	40	19	2
Right	Anterior cingulate cortex	3933	5.0	8	43	6
Left	Precuneus	2307	4.8	22	48	16
Left	Middle occipital cortex	1860	6.3	39	73	2
Right	Superior temporal gyrus	1719	3.9	52	10	3
Left	Thalamus	1570	4.1	4	17	16
Left	Middle orbitofrontal cortex	1321	4.2	24	44	18

Table 4 Areas of neural activation for positive and negative feedback on expert participants

Negative feedback processing (corresponds to the red color in the middle row of Fig. 3.1)

Right	Middle temporal gyrus	5328	5.5	67	43	9
Right	Middle cingulate cortex	1598	4.2	14	30	37
Left	Superior temporal gyrus	1551	5.0	56	4	5
Left	Caudate	1517	4.7	14	11	15
Right	Middle occipital cortex	1411	5.2	41	70	5
Right	Superior temporal gurus	1261	6.1	37	32	15
Right	Calcarine	1153	5.1	23	44	5
Right	Medial occipitotemporal gyrus	256	3.7	19	62	4
Left	Middle orbitofrontal cortex	188	3.8	67	15	7
Right	Insula	107	3.6	47	12	8

Table 5 Areas of neural activation for positive and negative feedback on novice participants

Positive feedback processing (corresponds to the blue color in the bottom row of Fig. 2)

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
Right	Precuneus	55621	7.3	6	58	49
Right	Middle temporal gyrus	20248	9.3	56	62	2
Right	Cuneus	8047	7.4	6	90	22
Left	Middle occipital cortex	7377	6.5	40	59	2
Right	Fusiform gyrus	6441	6.0	28	57	18
Left	Insula	3640	6.1	40	60	34
Right	Caudate	1415	5.8	9	11	6
Right	Precentral gyrus	672	4.9	38	2	42
Left	Middle orbitofrontal cortex	395	4.8	25	41	15
Left	Anterior cingulate cortex	223	4.7	11	42	3

Table 5 _ Areas of neural activation for positive and negative feedback on novice participants

Negative feedback processing (corresponds to the red color in the bottom row of Fig. 2)

Right	Middle temporal cortex	20826	7.38	56	51	4
Left	Cingulate	7058	5.6	9	16	9
Left	Middle frontal cortex	2345	5.0	38	37	32
Right	Middle frontal cortex	1629	4.6	28	59	19
Left	Superior temporal gyrus	985	4.2	48	2	3
Left	Centrotemporal cortex	925	4.5	62	8	6
Right	Thalamus	633	4.2	10	16	10
Left	Caudate	450	3.9	22	28	21
Left	Insula	368	3.7	30	22	2
Right	Superior orbitofrontal cortex	365	3.6	29	62	4

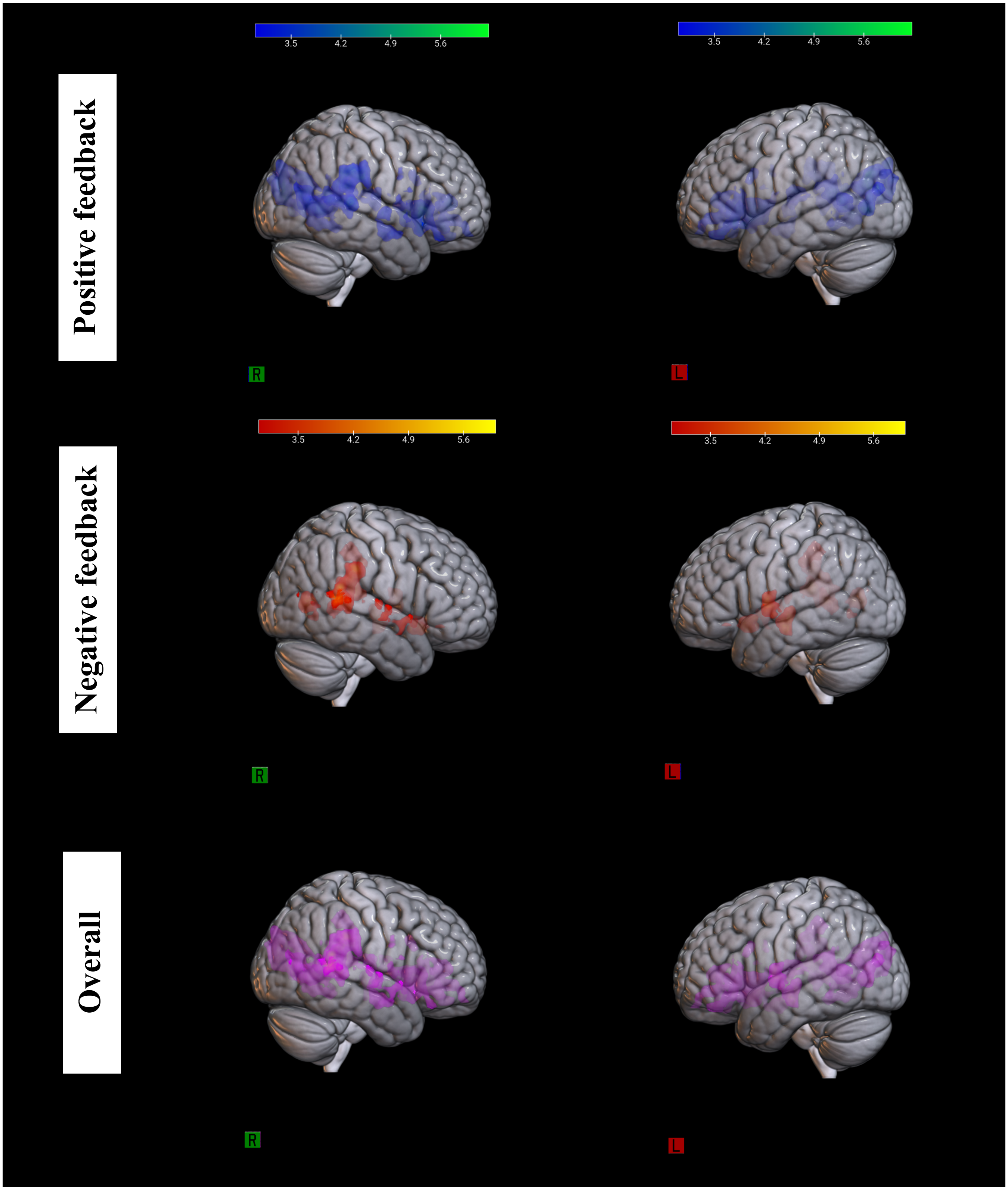

Figure 5 Neural activation in response to positive and negative feedback on expert participants. The image shows brain regions involved in feedback processing, including the brain regions listed in table 4.

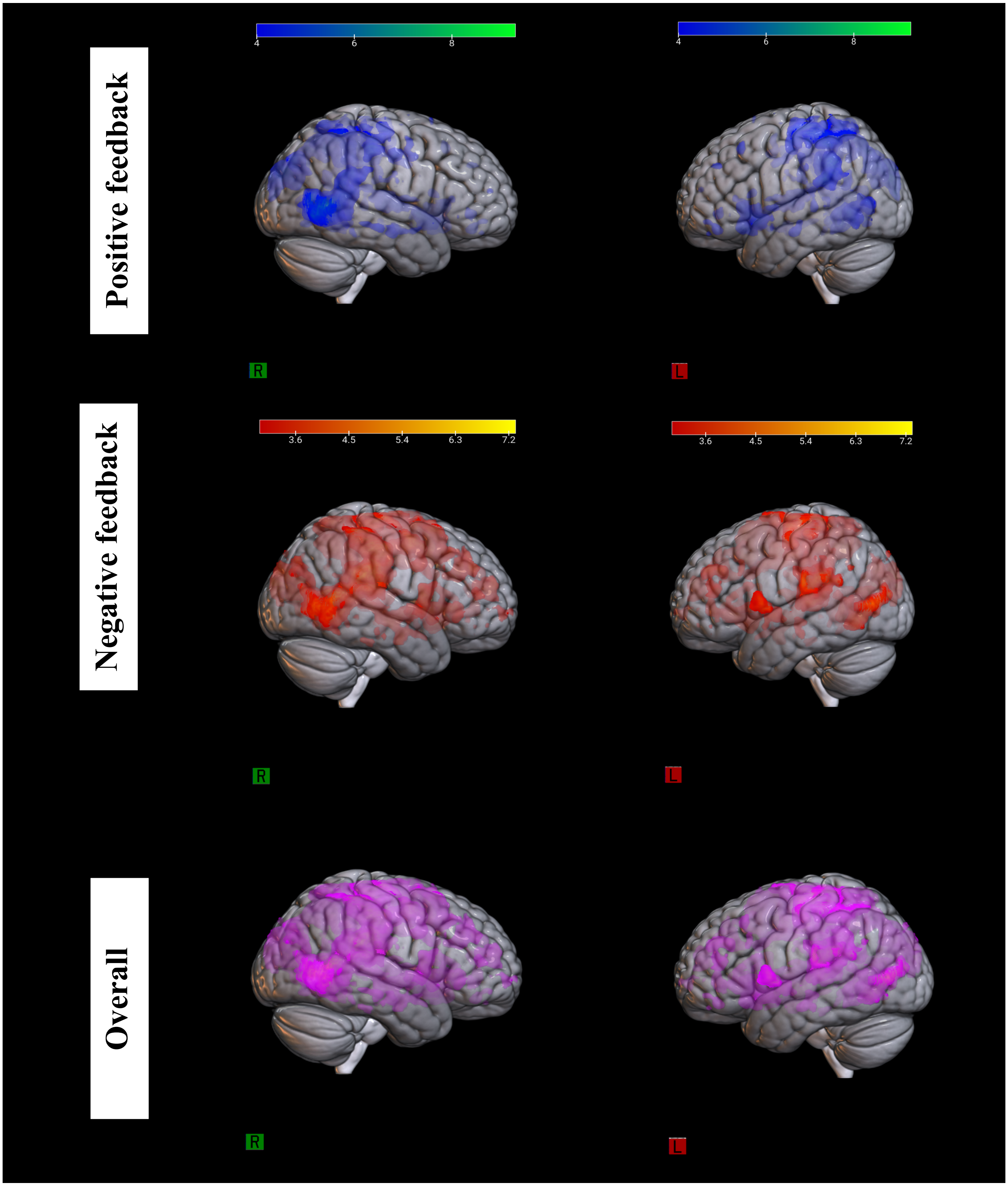

Figure 6 Neural activation in response to positive and negative feedback on novice participants. The image shows brain regions involved in feedback processing, including the brain regions listed in table 5.

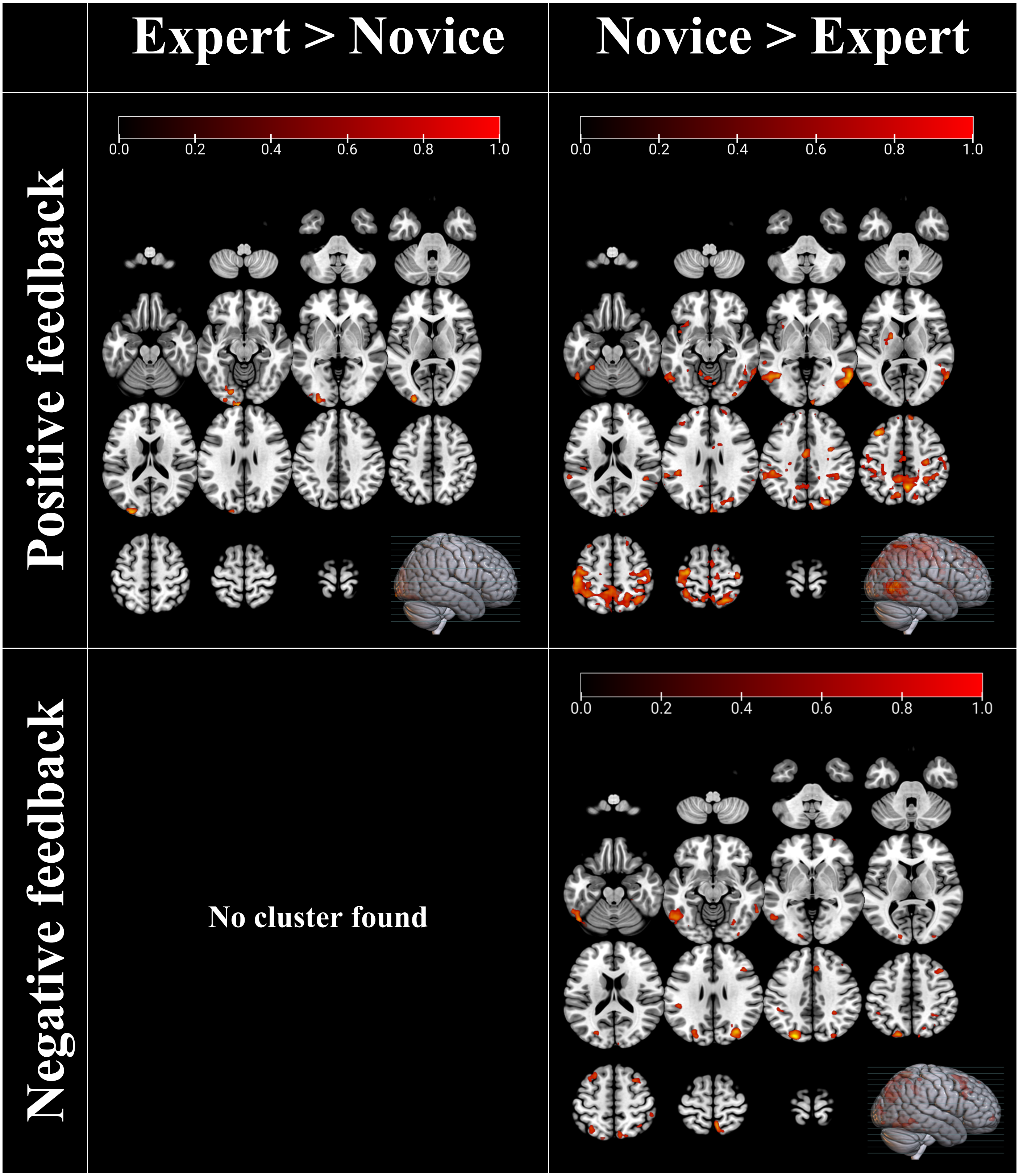

Figure 7 Neural areas of activation for positive and negative feedback in novice vs. expert participants. These results are based on between-group comparisons and highlight the differences in activation patterns between the two groups.

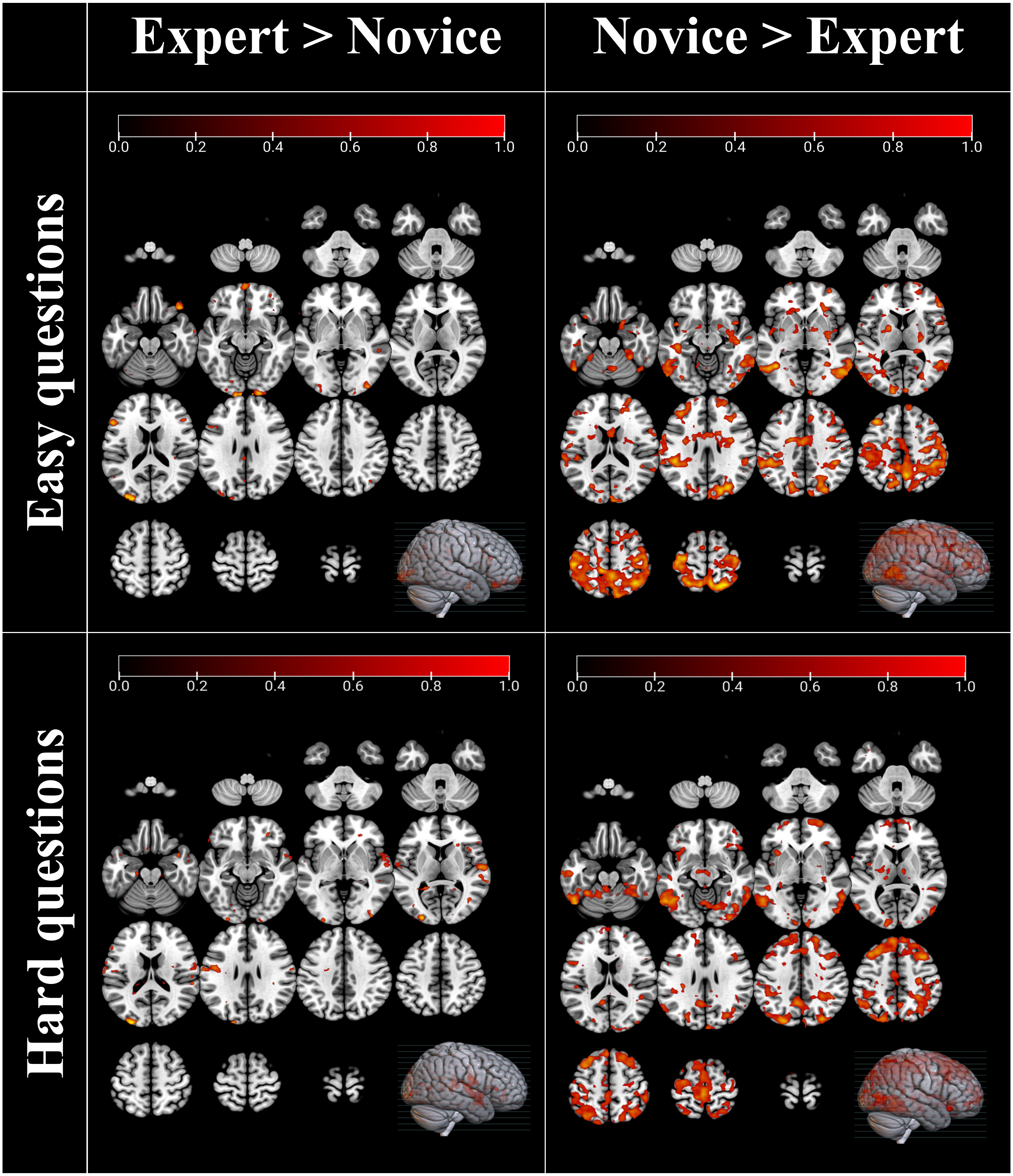

Figure 8 Neural areas of activation for hard and negative feedback in novice vs. expert participants. These results are based on between-group comparisons and highlight the differences in activation patterns between the two groups.

Chapter 4: General Discussion

Summary

Studies in neural areas of activation during clinical reasoning and decision-making play a critical role in improving medical education; however, the effect of feedback processing in clinical decision-making is poorly understood. In particular, differences in feedback processing in novice and expert clinicians during clinical decision-making. To understand this difference, we presented feedback (correct/incorrect diagnosis) to novice and expert clinicians after diagnosing simple or complex (easy, hard) cases while functional magnetic resonance imaging (fMRI) data were collected. Using a block design paradigm, we compared experimental blocks of feedback processing with rest blocks called fixation periods. Sixteen clinical cases (in the field of gastroenterology) were presented in the form of multiple-choice questions during an fMRI scanning session. The length of each clinical case was about 220 words, and they were shown using a projection system provided by Avotec Company. Feedback was presented to the participants at the last 20 seconds of the imaging trial after 10 seconds of the fixation period. To investigate neural activities of feedback processing, we contrasted the average signal of neural activity in feedback blocks against the average signal of neural activity in fixation blocks, where a greater activation level of feedback blocks can be associated with the cognitive load of feedback processing.

Providing feedback for clinical diagnosis evoked multiple neural activations in some cortical regions like the cingulate cortex, temporal lobe, striatum, Orbitofrontal cortex, and occipital cortex in novice and expert groups. Therefore, regardless of the type of feedback (positive or negative) and expertise level of participants (novice or expert), it seems some common brain regions are involved with feedback processing. Among those regions, the cingulate cortex (more specifically, ACC) is known for playing a role in reward processing and regulating reward-related behaviors. Therefore, as we hypothesized, feedback seems to have some reward/punishment component, and presenting feedback should evoke reward processing regions (ACC). On the other hand, the temporal lobe (medial temporal lobe, which includes hippocampi) is considered a vital memory structure alongside its critical role in language processing. As this brain area showed consistent activation in our study, feedback could be engaging with memory structure, whether learning new information or relearning/restructuring previous information. Moreover, the striatum (specifically the caudate nucleus) is another critical brain region for regulating different cognitive loads, including memory, learning, and motivation. Activation of the caudate nucleus by presenting feedback could indicate the involvement of feedback in learning, memory, and motivation. (Satterthwaite et al., 2007; McClure et al., 2003; Becker et al., 2014; Holroyd et al., 2005) . On the other hand, our ROI analysis validated the activation of specific brain regions that we hypothesized to be involved in feedback processing, such as the Orbitofrontal cortex (OFC), Prefrontal cortex (PFC), and Cingulate cortex. These findings provide additional support for the involvement of these regions in feedback processing during clinical decision-making.

A significant increase in activation of ACC, temporal lobe, striatum, and OFC in the novice group (relative to experts) for both positive and negative feedback suggests the novice group utilizes WM, motivation, and reward-related behaviors more than experts. This activation pattern could be because of the fact that novice groups are still in their medical learning phase and are more involved with memory formation and learning. Further investigation within each group (comparing positive vs. negative feedback) showed considerably more activation in the temporal lobe, ACC, and Caudate for positive feedback than negative feedback in both participant groups, suggesting higher effectiveness of positive feedback in memory and learning.

This study has some strengths, the first of which is the participant selection in expert and novice groups. This contrast between experts and novices is considered typical in the literature. The second one is the type of feedback (positive vs. negative FB) and the contrast between those two to see their specific effects on neural activation. Furthermore, the functional task itself is a well-designed task (greatly thanks to Dr. Kent Hecker's lab) that allowed us to look at different aspects of medical decision-making, including types of feedback (positive vs. negative FB), the effect of clinical case difficulty (hard vs. easy cases), and level of clinical expertise (expert vs. novice clinicians) all in one single task.

Limitations

Our study has a few limitations, from selecting participants to task design to the environment within fMRI. First and foremost, despite all the efforts, inside an MRI machine is not an ideal environment for cognitive tasks, and there is a number of problems, noises, and artifacts involved in the MRI studies. Yet, this is the best non-invasive neuroimaging tool at present. A second limiting factor in this study is recruiting expert participants in one specific medical field (gastroenterology), which narrows our task design to a clinical case only in gastroenterology cases. It is primarily due to the challenges in finding participants in a broader range of specialties.

Task performance and how we present the task to participants is also a limitation of this study. Since our task is based on a contextual explanation of a clinical case with some supporting analytic data about the task, the results do not represent other types of clinical tasks (visuospatial tasks as an example). On the other hand, feedback given to participants did not provide any descriptive information about the clinical diagnosis. Therefore, our results cannot be generalized to different types of feedback processing.

Future directions

This research aims to study the neural activations involved in the feedback processing of clinical decision-making. Therefore, this research could be a starting point to explore other feedback effects in clinical education using neuroimaging techniques.

The subsequent neuroimaging studies could take advantage of other neuroimaging modalities with higher temporal resolution (Electroencephalography, EEG) combined with high spatial resolution data of fMRI. Conducting this study can help us better understand the spatiotemporal correlation of neural regions involved in feedback processing.

One important direction for future studies, which is highly beneficial for understanding information structure in the long term, is to study the effect of feedback in a longitudinal neuroimaging experiment. The question is how neural areas involved with feedback processing vary over time. As we looked at two groups of clinicians, one with no/little clinical experience and one with a good experience level, it is worth studying how brain activity pattern changes during medical schooling and how gaining experience affects feedback processing.

Conclusion

This study suggests the difference in brain regions activation for processing positive versus negative feedback in clinicians with different levels of expertise for hard and easy clinical cases. Clinician level of expertise (Expert vs. novice clinicians) seems to cause additional neural activation in feedback processing tasks and indicates that in novice clinicians, brain activations were consistent with areas identified in studies referred to earlier. Our findings suggest a commonality between neural activation regions in both groups of participants; however, the novice group showed a more extensive activation cluster size in those common areas (Figure 4 - 9). Our findings also show that positive and negative feedback have different effects and activate other brain regions in our study group. With respect to the impact of clinical case difficulty in feedback processing, our results show some lateralization in neural activities.   Overall, this study suggests that feedback is associated with learning, reward processing, and memory. Differences in activation regions between the two groups of participants highlight that the novice group demands more working memory, motivation, and reward processing. Significant activation of OFC shed light on the critical role of feedback in learning and decision-making.

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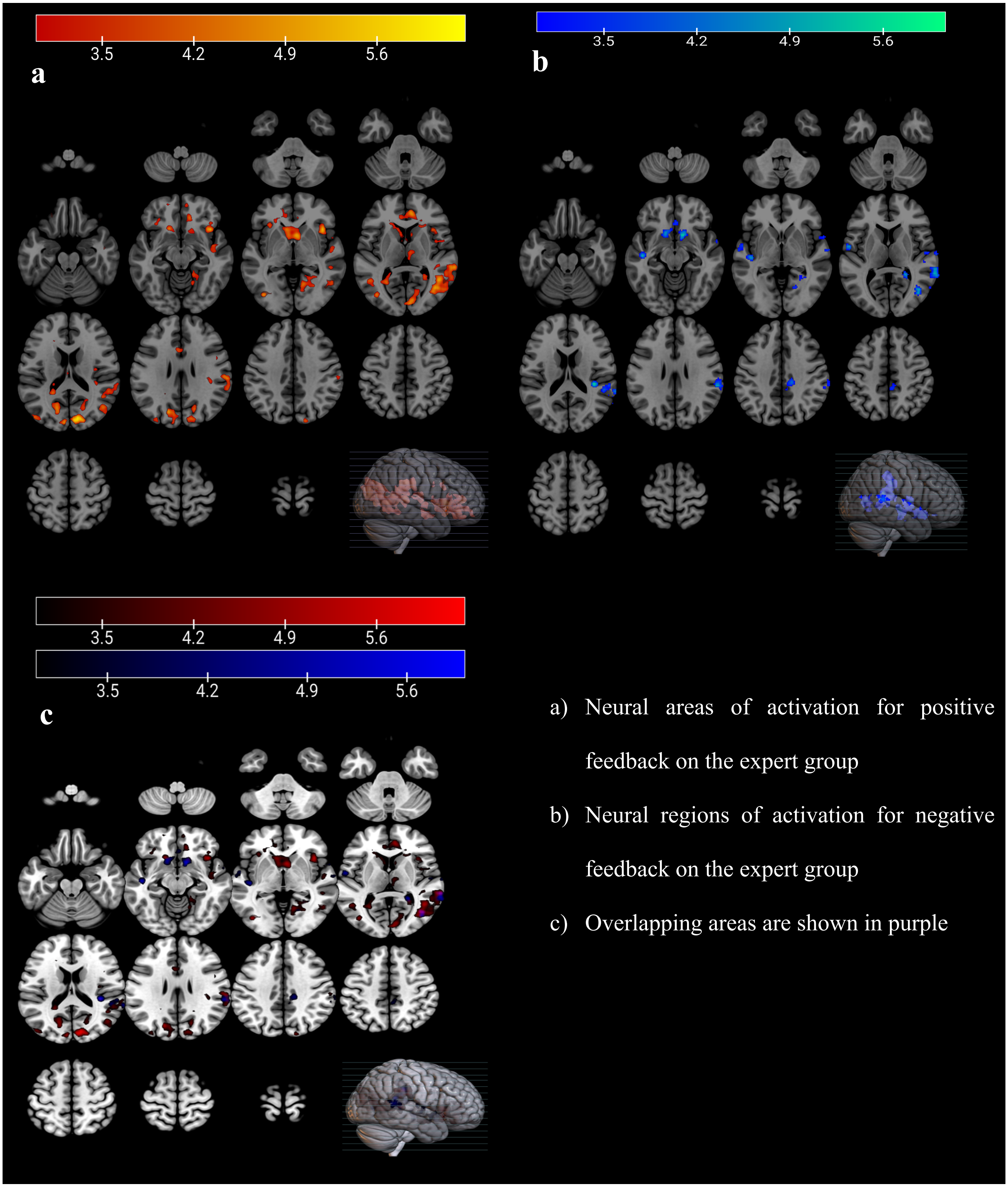
Appendix A: Supplemental figures

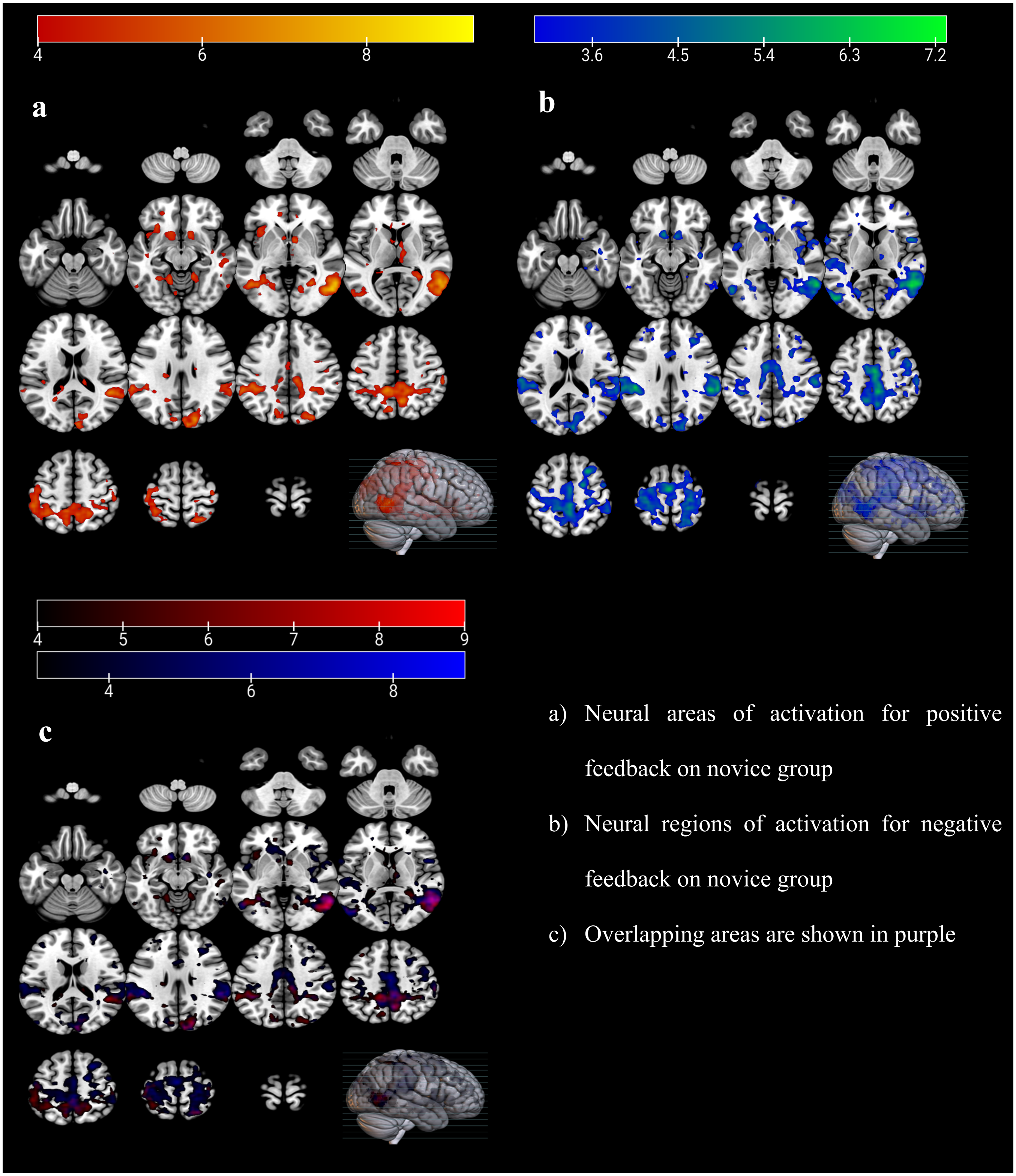


a) Neural areas of activation for positive feedback on the expert group

b) Neural regions of activation for negative feedback on the expert group

c) Overlapping areas are shown in purple

Figure 9 A1 Neural activation in response to positive and negative feedback on novice participants. The image shows brain regions involved in feedback processing, including the brain regions listed in table 4.



a) Neural areas of activation for positive feedback on novice group

b) Neural regions of activation for negative feedback on novice group

c) Overlapping areas are shown in purple

Figure 10 A2 Neural activation in response to positive and negative feedback on novice participants. The image shows brain regions involved in feedback processing, including the brain regions listed in table 5.

Appendix B: Supplemental tables

Table 6 _ B1 Areas of neural activation for positive feedback where experts have greater activation than novices (Positive feedback, Expert>Novice).

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
Left	Middle occipital cortex	3690	6.5	-26	-93	4
Left	Cerebellum	1129	5.2	-18	-85	-17

Table 7 _ B2 Areas of neural activation for positive feedback where novices have greater activation than experts (Positive feedback, Novice>Expert)

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
Right	Middle temporal cortex	2783	6.7	60	-59	2
Right	Superior parietal cortex	2263	602	24	-60	64
Right	Precuneus	2163	6.1	6	-58	50
Left	Middle frontal cortex	776	6.2	-36	24	47
Right	Superior occipital cortex	529	5.5	28	-80	40
Right	Fusiform	114	5.0	45	-64	-20
Left	Insula	63	4.3	-42	8	-8

Table 8 _ B3 Areas of neural activation for negative feedback where experts have greater activation than novices (Negative feedback, Expert>Novice)

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
No cluster						

Table 9 _ B4 Areas of neural activation for negative feedback where novices have greater activation than experts (Negative feedback, Novice > Expert)

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
Left	Inferior temporal cortex	5642	6.5	-56	-62	-8
Left	Superior occipital cortex	5068	7.4	-24	-82	38
Right	Precuneus	2470	6.1	3.9	-54	64
Left	Middle frontal cortex	1030	5.1	-28	24	53
Left	Superior parietal cortex	683	5.1	-30	-62	59
Right	Fusiform	583	5.6	32	-72	-16
Right	Inferior frontal cortex	452	5.1	42	24	28
Right	Middle orbitofrontal cortex	324	5.0	30	60	-7
Left	Calcarine	130	4.7	6	-96	14
Right	Inferior temporal cortex	356	5.0	60	.52	.12

Table 10 _ B5 Areas of neural activation for feedback on easy questions where experts have greater activation than novices (Easy questions, Expert > Novice)

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
Left	Middle occipital cortex	1314	7.2	-24	-96	22
Right	Calcarine	513	6.2	18	-100	-12
Right	Inferior orbitofrontal cortex	653	6.1	40	33	-20
Right	Inferior occipital cortex	398	5.7	38	-90	-3
Right	Middle temporal cortex	102	4.4	64	-4	-23

Table 11 _ B6 Areas of neural activation for feedback on easy questions where novices have greater activation than experts (Easy questions, Novice > Expert)

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
Right	Superior parietal cortex	20159	8.1	24	-60	64
Left	Middle frontal cortex	8836	7.0	-36	24	47
Left	Fusiform	259	6.0	-34	-77	-14
Right	Inferior occipital cortex	209	5.5	35	-88	-12
Right	Insula	1055	5.1	26	30	-4
Right	Hippocampus	602	4.5	22	-34	10
Left	Caudate	2225	4.3	-10	28	-2
Right	Thalamus	471	4.2	12	-2	-1
Right	Amygdala	170	3.8	18	2	-10

Table 12 _ B7 Areas of neural activation for feedback on hard questions where experts have greater activation than novices (Hard questions, Expert > Novice)

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
Right	Superior temporal cortex	6509	5.6	56	-12	10
Left	Middle occipital cortex	3785	6.8	-28	-96	18
Left	Precuneus	1045	4.8	-22	-46	5
Right	Middle orbitofrontal cortex	365	4.2	28	40	-12
Right	Inferior frontal cortex	241	4.0	52	28	6
Right	Calcarine	164	4.6	20	-50	6
Left	Hippocampus	137	4.4	-34	-4	-26
Left	Thalamus	97	4.0	-10	-28	16

Table 13 _ B8 Areas of neural activation for feedback on hard questions where novices have greater activation than experts (Hard questions, Novice > Expert)

Cerebral hemisphere	Neural area of activation	Cluster size (Number of activated voxels)	Max Z (Maximum statistic value)	MNI coordinates		
				X	Y	Z
Left	Middle frontal cortex	14137	8.5	-28	26	52
Left	Inferior occipital cortex	3552	10.3	-48	-64	-18
Left	Middle temporal cortex	2375	6.3	-56	-16	-20
Left	Insula	1932	5.5	-34	14	-4
Left	Thalamus	1097	4.7	-22	-12	6
Right	Putamen	771	4.3	24	-1	3
Right	Hippocampus	650	4.5	32	-26	1
Left	Anterior cingulate cortex	126	3.7	-4	45	10