Automated Design of fMRI Paradigms

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Abstract

Neuroimaging techniques have been widely used in recent decades to assess brain activation patterns for neuroscience. Task design is the most important challenge for neuroimaging studies, to achieve the best modeling for assessing brain patterns within and across subjects. Specifically, functional magnetic resonance imaging (fMRI) experiments rely on the precise and effective design of sequences of stimuli intended to activate specific brain regions (i.e. paradigm design). In this paper, we use PDDL+ to model fMRI paradigms so that neuroscientists can use automated planning to design neuroimaging paradigms in a declarative way. Planning neuroimaging paradigms is especially important for functional studies and presurgical planning. The former should help to ensure an experimental design that allows the analysis of the brain regions that are interesting in the study. The latter should help surgeons select the correct stimuli for a presurgical, non-invasive, exploration of the cognitive functions that might be affected by debridement of brain lesions.

Introduction

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive technique widely used to analyze brain functions (Glover 2011). This imaging technique measures neuronal activity by detecting concentration changes of oxy- and deoxy-hemoglobin in the stimulated area (Pauling and Coryell 1936). This is an indirect measure called Blood Oxygen Level Dependent (BOLD) or hemodynamic response (Ogawa and Lee 1990; Logothetis and Wandell 2004). In order to develop an fMRI study a researcher starts with a research question concerning either brain function or an anatomical region of interest. Using the research question as guidance, researchers design an fMRI protocol, which includes various imaging parameters, but importantly for this work, it also includes an fMRI paradigm. Paradigms are the activities performed or stimulus received by the subject during a study (Amaro Jr and Barker 2006) to evoke hemodynamic response or brain activation in certain brain areas. The brain areas evoked in an exam are possibly related to the research question, due to functional differences between subjects. Common paradigms include visual, motor, language and memory, each of which include a series of possible tasks or stimuli designed to activate the respective brain regions. In order to activate the brain area of interest, researchers select a paradigm expected to increase the BOLD signal of those regions (Logothetis and Wandell 2004).

Since there are extensive study designs and software available for fMRI projects, researchers often build new fMRI protocols by choosing available paradigm designs that they can combine in a way that helps them answer their own research question (Amaro Jr and Barker 2006; James et al. 2014). Alternatively, researchers design new paradigms when they fail to find an existing one. In both cases, the researcher's task consists of conducting a literature review of studies related to their research question and then picking existing paradigms or choosing ones that could be adapted in creating a new one. Ultimately, a successful fMRI experiment relies on precise and effective paradigm design, while at the same time aim to minimize its overall cost of each scan.[1] Thus, we develop an application of automated planning in order to solve the dual problem of effective paradigm design and scan cost minimization. Our key contributions are then a formalization of fMRI paradigm design in PDDL+, an application of automated planning for neuroscience research and presurgical planning, and a tool for automatic stimuli generation for fMRI scans.

Background

Design of fMRI Studies

During an fMRI task, there is an increase in neuronal activity in the brain area associated with that task. For example, during a motor skill task, there is neuronal activation in the motor area. A paradigm is a temporal allocation of stimuli to acquire BOLD responses in the desired areas of a subject's brain (James et al. 2014). Block- and event-related designs are the most used and efficient approaches to paradigm design, as shown in Figure 1. In the first approach, each block is presented for relatively long alternating periods where the cognitive state is maintained. Event-related designs are composed by discrete events, where the stimuli is presented for shorter alternating periods and used to decomposition of cognitive states (Logothetis 2008) The stimuli can be, for

[1]The cost of an fMRI scan is directly proportional to the time it takes, due to the substantial power requirements of maintaining an fMRI scanner's superconducting magnets.

example, auditory or visual, and is presented for a certain amount of time. The stimulation period is alternated with a control period in order to return the neuronal activation to its basal state. A paradigm can contain a variety of tasks blocks or events, usually showing the same more than once to ensure a consistent BOLD response in the regions of interest (Newman, Twieg, and Carpenter 2001).

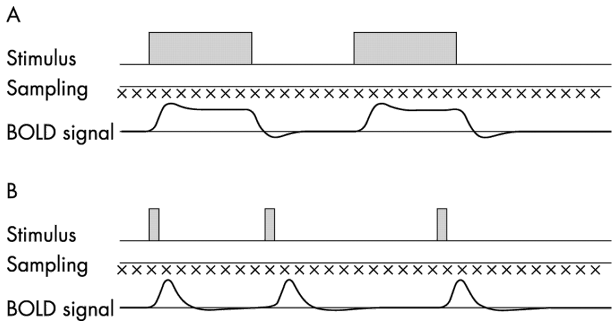


Figure 1: Block (A) and Event-related (B) paradigm designs (Matthews and Jezzard 2004)

Specialized software, such as Psychopy (Peirce 2007), presents stimuli from a paradigm to a subject. Psychopy is a free suite of software tools written in Python designed to make the generation of experimental stimuli easier, using the latest advances in hardware and software.

Presurgical Planning Using fMRI

The localization of important cortical and subcortical areas at risk of injury during the surgical removal of brain tumors or other resectable lesions is important to avoid permanent damage to neurological function (Acharya and Dinner 1997; Sharan et al. 2011). The Intracarotid Amobarbital Test (IAT or Wada test) is universally relied on as a prognostic test for patients with intractable temporal lobe epilepsy who are candidates for neurosurgical intervention. The Wada test involves the temporary inactivation of one cerebral hemisphere by the injection of sodium amobarbital (Acharya and Dinner 1997; Sharan et al. 2011) and has been used for more than half a century to determine language dominance. However, this test has a major shortcoming due to its invasiveness with lack of standardization and absence of spatial resolution. Potential complications include encephalopathy, stroke, vessel dissection, and seizure (Loddenkemper, Morris, and Möddel 2008). By contrast, clinical usage of fMRI in presurgical planning is becoming a standard tool to avoid neurological impairment during surgery providing a finer spatial relationship between the lesion and brain functionality. Such planning involves using fMRI to map brain areas involved in several functions, such as language and memory, and offers diagnostic information non-invasively before surgery and with justifiable clinical expenditure (Tieleman et al. 2009). Using fMRI-based planning, the surgeon just needs to plan with an fMRI neuroscientist a paradigm with a set of stimuli. As fMRI is a repeatable procedure, it would be advantageous to create validated paradigms to allow its use in lieu of the Wada test. Thus, we design planning domains for the most common neurological functions localized in presurgical planning: language dominance and lateralization, motor and memory skills (Ries et al. 2004; Sunaert 2006; Loddenkemper, Morris, and Möddel 2008).

Temporal Numeric Planning

Classical planning treats the time as relative (Fox and Long 2003) and takes into account only causal dependencies between actions. However, real-world problems often involve characteristics such as time, numbers, stochastic effects and dynamic environments. Numeric planning extends classical planning with numeric state variables and uses languages such as PDDL 2.1 (Fox and Long 2003) and PDDL+ (Fox and Long 2006). These formalisms allow modeling time-dependent change as discrete time-dependent effects of durative actions or as continuous process-dependent change. PDDL+ is the extension of PDDL for modeling hybrid systems through the use of *continuous processes* and *events* (Haslum et al. 2019). It is intended to support the representation of mixed discrete-continuous planning domains. The Expressive Numeric Heuristic Search Planner (ENHSP) (Scala et al. 2016, 2017) supports both PDDL 2.1 and PDDL+. ENHSP is a forward heuristic search planner and transforms the PDDL into a Asymptotic Relaxed Planning Graph (ARPG). Nodes represent states visited by the planner and the search in the graph is guided by a heuristic function to explore only those nodes whose associated state is reachable from the initial state and reaches states closer to the goals.

Modelling fMRI Studies in PDDL+

In this section we introduce the model that is the basis of the PDDL+ representation of fMRI paradigm planner problem. We automatically derive planning domains representing the relation of stimuli in fMRI paradigm with the various anatomic cerebral regions for presurgical planning. We analyze the brain activation areas performing a *t-test* for each block and event stimulus in the Analysis of Functional NeuroImages (AFNI) software (Cox and Hyde 1997; Gold et al. 1998). We use a dataset of fMRI studies available in the Brain Institute (BraIns) of Rio Grande do Sul, with whom we have a long term collaboration. Our model was described based on six different paradigms, the most used in the fMRI research.

For this paper we use a simplification of PDDL+ planning problem is a tuple $\langle P, V, A, P_s, E, I(P,V), G(P,V)\rangle$, in which P is a set of propositions, V is a vector of real variables and A is a set of durative and instantaneous actions, P_s is a set of processes, and E a set of events. $I(P,V)$ and $G(P,V)$ represent the initial state and goal condition respectively (Cashmore et al. 2016). The set of propositions P and variables V induce a state space, over which we assume an entailment relation $\mathrm{s} \models cond$ that denotes whether a state s supports a certain condition $cond$.

We represent an action as a tuple $\mathrm{a} = \langle name, pre, \mathit{eff}\rangle$ where $name$ is the name of the action, pre is a precondition and eff is an effect, comprising a positive part eff^+, a negative part eff^-, and a numeric part $\mathit{eff}^{\mathbb{R}}$. We say an action is applicable in a state s if s $\models$ *pre*. Updates to the symbolic part of a state ($\mathit{eff}^+ \cup \mathit{eff}^-$) occur using set operations, removing elements of eff^- and adding elements of eff^+. Changes to the numeric part of a state occur by directly updating variables mentioned in $\mathit{eff}^{\mathbb{R}}$, yielding a new numeric part $\mathit{eff}^{\mathbb{R}'}$ with updated values for all $v \in \mathit{eff}^{\mathbb{R}}$. The application of an action a at a state s results in a new state $s' \leftarrow (s - \mathit{eff}^-) \cup \mathit{eff}^+ \cup \mathit{eff}^{\mathbb{R}'}$. Events are tuples $\langle cond, \mathit{eff} \rangle$ where $cond$ is the triggering condition of the event, and eff are the changes that take place in s′ automatically once $cond$ holds in s All fMRI experiments begin with an instruction screen, presented to prepare the subject for the performed paradigm. The instructions were modeled as a single *action* $\langle BeginExperiment, \{\neg instructions\}, \{(time \leftarrow time + 10), instructions, \neg rest\}\rangle$, executed in the beginning of all experiments. The time is increased by 10 seconds, which is the usual block time for instructions.

Key to our modeling of the paradigms is predicting neural activation in the regions of interest for the study at hand. Thus, we represent each planner *action* that describes the fMRI stimuli as $\langle Stimulus(ST), \{rest, instructions\}, \{(intensity(R) \leftarrow intensity(R) + X), (time \leftarrow time + Y), \neg rest\}\rangle$, where R is a vector of regions activated by the stimulus ST, X is the activation intensity of each region R and Y is the time that the block or event B is displayed on the screen. In this paper, we modeled the intensity X empirically for domain modeling purposes, but these values should be learned from fMRI datasets.

Between the presentation of the stimuli, small rest intervals are presented. These usually last 1 to 2 seconds and were modeled as *actions* $\langle BaselineRest, \neg rest \wedge instructions, (intensity(R) \leftarrow intensity(R) - X) \wedge (time \leftarrow time + Y) \wedge rest\rangle$. In this case, R is a vector of all brain regions, and the rest intervals result in a decrease of X units in the activation intensity in all brain regions. We model long rest intervals during the experiment as *events*, allowing the neuronal activation to return to its basal state. The baseline *event* is represented by a tuple $\langle (time = W), (intensity(R) \leftarrow intensity(R) - X) \wedge (time \leftarrow time + 30)\rangle$. The baseline event happens when the total time of the experiment reaches time Z.

The PDDL+ instance was described initializing activation intensities of brain regions and experiment time to zero. Altogether, 22 brain regions were considered, these being those found in the statistical analysis performed. We use the $: metric$ to minimize the total experiment time, as this is an important variable when planning the paradigms. The planner *goals* were defined as $\langle intensity(R) >= X\rangle$, setting the minimum number of active *voxels* X desired for the regions R of interest.

Automated Planning for Presurgical Planning

The main contribution of this work is an automatic mechanism that allows a surgeon to assess cognitive activities related to areas at risk of injury during the surgical remove of brain tumors or resectable lesions. As an example of the importance of presurgical planning, consider one case report of an adolescent patient with an intractable epilepsy (Ries et al. 2004). The patient had a left congenital temporal lobe tumor, a structural abnormality near cortical language areas. The clinical recommendation was for the removal of the tumor in hopes of achieving seizure control and without interfering with the neurologic and neuropsychological function. This patient underwent both Wada and fMRI procedures before neurosurgical removal of the tumor. The fMRI was performed to determinate the language dominance and lateralization of language functioning. Figure 2 shows the activations from a subvocal reading task, where the patient silently read short stories and was instructed to attend to each word. The figure shows the tumor, indicated by the arrow, the left-sided activation of frontal language areas (A) and right-sided activation of frontal and temporal language areas (B).

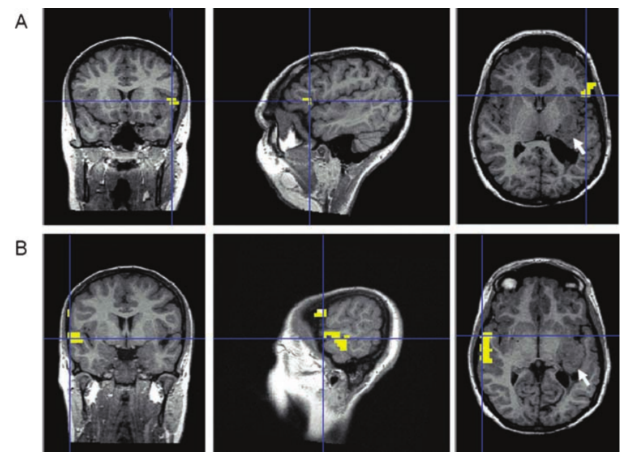
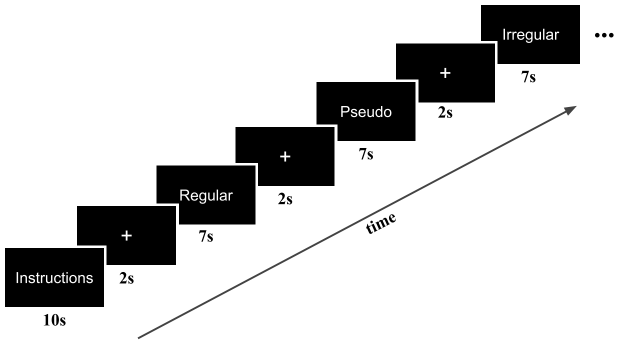
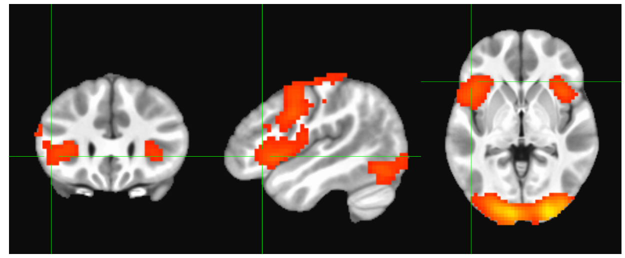


Figure 2: Presurgical example of brain activation during reading task on a clinical case. The tumor is indicated by the arrow. (Ries et al. 2004)

We compare our presurgical planning domain with the results obtained by the actual fMRI scan used for presurgical planning of our example, shown in Figure 2. In order to generate the paradigm for the fMRI presurgical planning, we set the Left Inferior Frontal Gyrus (LIFG) as the planner's goal: $\langle intensity(LIFG) >= 100\rangle$. LIFG plays a key role in the cerebral cortical network that supports reading and visual word recognition (Cornelissen et al. 2009). We chose this region because it is one of the regions responsible for language processing, comprehension and production (Marslen-Wilson and Tyler 2007). The paradigm obtained by the planner can be seen in figure 3a, and it is a language paradigm that uses visual words stimuli. Each stimulus consists of sequences of words divided between the classes regular, irregular and pseudo words are presented. For each word, the subject responds with buttons if the word presented exists or not. Figure 3b shows the average brain activation of 100 participants who performed this paradigm in fMRI. The cursor points to activation in the LIFG region and a right-sided activation of frontal language areas and occipital lobe activation can also be observed in the figure. The presence of occipital activation is common because it is a region of the visual cortex.



(a) Language stimulus paradigm



(b) Activations obtained by the stimulus

Figure 3: A language paradigm obtained to LIFG region as planner's goal. (a) The stimuli is presented in a black screen with white letters and the exam starts with respective paradigm instructions. Every screen with "+" is a rest time, followed by a presentation of regular, irregular or pseudo-words. (b) Brain's activations from this paradigm.

Consistent with Wada, fMRI predictions and our fMRI paradigm planner, the removal of the mesial temporal tumor did not result in significant loss of language or verbal memory functioning. The assessment was made one year after the surgery, that was made with preservation of left-sided cortical structures, as hippocampus, amygdala and parahippocampal gyrus. The Wada test failed to provide data about the localization of language function, just lateratization. This demonstrates the value of fMRI activity during language testing and the potential of fMRI to provide new insights into brain functional organization for patients treated for epilepsy (Ries et al. 2004). The paradigm planned by our domain obtained results very similar to those obtained in the fMRI exam carried out in this clinical study.

Experiments and Results

We developed a script to generate a PDDL+ domain and instance for ENHSP, read the ENHSP output and generate a *csv* file with the stimulus sequence created by the planner. After generating the sequence of stimuli, we convert it so that it is presented to the subject during the resonance exam. To present such paradigm, our script uses the Psychopy software and generates the corresponding paradigm from the *csv* file, being ready to be used during the fMRI exam.

As a second example, we set the Superior Temporal Gyrus (STG) as the goal: $\langle intensity(STG) >= 100\rangle$. STG is part of auditory association cortex (and a site of multisensory integration) and thus necessarily plays some role in spoken word recognition (Zevin 2009). The Figure 4 shows the generated paradigm. The planned paradigm uses audio tasks, and it is composed by "Speech" and "Vocod" stimuli. The first consists of the presentation of words audio and the second of incomprehensible audios, called vocoded speech. During auditory stimuli, the subject does not receive any visual stimuli, only the presence of the black screen on the monitor.

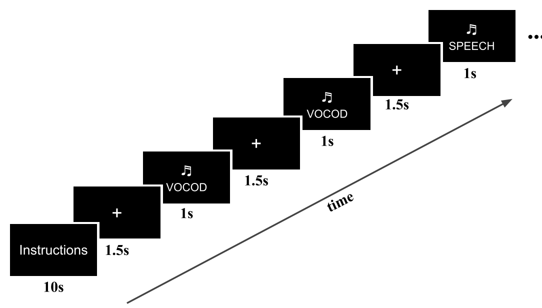


Figure 4: A auditory paradigm obtained to STG region as planner's goal. The exam starts with respective paradigm instructions. Word and vocoded audios are displayed while a black screen is on the monitor.

Conclusions

We developed a specific application in PDDL+ to planning neuroimaging paradigms in order to solve the dual problem of effective paradigm design and scan cost minimization. Empirical experimentation shows that our planner successfully generates a valid presurgical planning paradigm that approximates the activations expected of a manually designed paradigm. The current version of our paradigm planner uses empirical values of brain activation intensity based on data from six different functional magnetic resonance paradigms. Future work will involve mathematical modeling of the hemodynamic response to brain activation to determine the approximate activation values for each stimulus presented, and possibly use plan recognition to verify compliance during a study (Pereira et al. 2016). At the moment we are gathering a large dataset of presurgical plans in order to derive the specific regional activations in a data-driven fashion.

In conclusion, our approach provides the basis for using automated planning in the context of designing fMRI paradigms. Moving forward, we expect this application to become a useful tool for Neuroscientific research and as a supporting resource for presurgical planning.

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