

# Combining an Operant Chamber Paradigm with [18F]Fluorodeoxyglucose MicroPET Imaging: A Study on Conflict Processing in the Rat

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## ABSTRACT

Response conflicts occur when spatial features of a stimulus, although task-irrelevant, are incongruent with spatial features of the response, which leads to longer reaction times and higher error rates (Simon effect). To identify brain areas relevant for conflict processing as well as associated neuronal mechanisms in rats, we combined auditory Simon tasks in an operant chamber with positron emission tomography (PET). As tracer we used [<sup>18</sup>F]fluorodeoxyglucose (FDG), which accumulates in active cells and therefore allows to perform the PET scan (FDG-PET) after the rat has completed the cognitive task. Rats showed a robust Simon effect including sequential modulation, similar to the findings in human participants. Our subtractive as well as correlative analyses of PET data revealed that a prefrontal cortical area, the prelimbic cortex, the striatum, and the premotor area M2 were involved in conflict processing. The results of this study support the dual route model established for the processing of response conflicts.

## Author Keywords

microPET, imaging, operant chamber, Simon task, conflict processing, conflict monitoring.

## INTRODUCTION

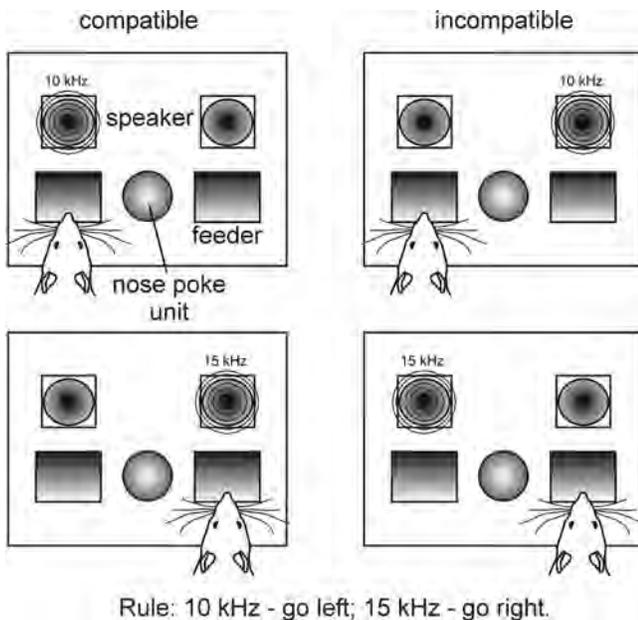
*Everyday's activities such as writing an e-mail during a telephone call or driving a car while talking to a fellow passenger lead to conflicts in the cognitive system. Such phenomena are characterized by conflicting results of **parallel information processing, which leads to higher** reaction times and increased error rates. It is thought that the dorsal anterior cingulate cortex is involved in monitoring such conflicts and prefrontal areas in resolving them [5]. However, the exact location of involved brain areas are not known so far. Recently, it was shown that rats are able to perform an auditory conflict task, which generates a Simon effect [1]. The Simon effect is a neuropsychological interference effect in which reaction times are longer and errors more frequent when spatial features of the stimulus (although task-irrelevant) are inconsistent with spatial attributes of the response [7]. A dual route model has been proposed to explain the Simon effect [2]: A fast automatic route processes task-irrelevant stimulus location and selects a response directed towards the stimulus, whereas a slower intentional route uses the relevant stimulus feature to select the appropriate response established during training. The resulting response conflict delays performance in the current trial and initiate conflict monitoring and resolution mechanisms, which reduce conflict effects in the next trial (sequential effects, [3,8])*

To study the neural basis of conflict processing in animal models, invasive techniques like brain lesions or pharmacological manipulations have frequently been used. However, brain imaging has the advantage of displaying focal activity of the entire brain in intact animals. While fMRI is not suitable for tasks where the animals are required to move freely, it was recently shown that combining microPET imaging using FDG-PET in combination with a behavioural task is suitable to study

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**Figure 1. Positions of inputs and outputs of the operant chamber for the auditory Simon task.**

stress in rats [4,9]. In the current experiment, we set up an auditory Simon task for rats in an operant chamber, which can be easily combined with microPET imaging to study the functional anatomy of conflict processing.

#### BEHAVIOURAL TASK

Measuring reaction times in rodents is difficult because whole body movements are required for responses and therefore large individual differences occur. To overcome this problem, we developed a nose poke-induced Simon paradigm (Figure 1) placed in an operant conditioning chamber (Med associates Inc. Georgia, VM, USA).

Eight Lister hooded rats (*Rattus norvegicus*) were trained to perform an auditory Simon task. Auditory stimuli were presented unilaterally, and response side (left/right) was indicated by stimulus pitch (10 kHz, 15 kHz; relevant stimulus feature). When stimulus and correct response were on the same side, this was defined as a non-conflicting condition (compatible). In conflicting trials (incompatible), stimulus and required response were on opposite sides. Reaction times and error rates were measured. Four animals performed four different tests each combined with microPET. In the control task, sound was presented bilaterally (neutral task  $T_N$ ).  $T_C$  consisted of 100 % compatible trials, and  $T_I$  of 100 % incompatible trials. In  $T_R$ , 50 % compatible and 50 % incompatible trials followed each other randomly.

#### MICROPET

The animals received an intraperitoneal injection of 2 mCi FDG during a brief anesthesia. After five minutes, rats performed a Simon task in an operant chamber for 30 min. During this period FDG was taken up by glucose

transporters, phosphorylated by hexokinase but not further metabolized and therefore accumulated in cells with high metabolic activity. MicroPET scans took place under isoflurane inhalation anaesthesia in a Focus 220 microPET scanner (CTI/Siemens Knoxville, TN) with a resolution at center of field of view of 1.4 mm. Emission data were taken over 30 min starting 60 min after FDG injection. Following Fourier rebinning, data were reconstructed using OSEM3D/MAP reconstruction [6] resulting in voxel sizes of 0.38 x 0.38 x 0.82 mm. To rule out gross structural brain anomalies and to provide individual templates for co-registration of the PET images, T2-weighted structural MR images were acquired. MRI and PET data were analyzed with the help of the imaging tool VINCI [10].

#### RESULTS

As predicted, we observed significantly shorter reaction times as well as lower error rates in compatible compared to incompatible trials. Furthermore, we could demonstrate sequential modulation, i.e., a Simon effect was only present if the preceding trial was compatible. The analysis of the PET data revealed different activation patterns for different task settings. We detected increased metabolic activity in the right prelimbic cortex during  $T_I$  and  $T_R$  compared to  $T_N$ , indicating that this region is involved in conflict processing. Additionally, a part of the left striatum displayed decreased activation during  $T_I$  and  $T_R$ , which may be related to the suppression of unwanted movements. During  $T_I$ , metabolic activity of both left and right anterior premotor cortex was positively correlated to error rate, indicating that animals with high aM2 activity were prone to errors.

#### CONCLUSION

FDG-PET using high resolution microPET scanners is a promising technique to study the metabolic activity of brain areas related to conflict processing in small animals. We have identified a prefrontal area, the prelimbic cortex, to be involved in conflict processing, which is in line with human findings. Furthermore, our results are in accordance with the dual route processing model. Because rats show robust Simon effects including sequential modulation, they are suitable animal models to investigate conflict monitoring as well as conflict resolution processes and its modulation by brain function disturbances such as stroke.

All animal procedures were in accordance with the German Laws for Animal Protection and were approved by the local animal care committee and local governmental authorities.

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