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Review Article

Caffeine and Cognition in Functional Magnetic Resonance Imaging

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Abstract. Caffeine has been consumed since ancient times due to its beneficial effects on attention, psychomotor function, and memory. Caffeine exerts its action mainly through an antagonism of cerebral adenosine receptors, although there are important secondary effects on other neurotransmitter systems. Recently, functional MRI (fMRI) entered the field of neuropharmacology to explore the intracerebral sites and mechanisms of action of pharmacological agents. However, as caffeine possesses vasoconstrictive properties it may interfere with the mechanisms underlying the functional contrast in fMRI. Yet, only a limited number of studies dealt with the effect of caffeine on measures in fMRI. Even fewer neuroimaging studies examined the effects that caffeine exerts on cognition: Portas and colleagues used fMRI in an attentional task under different levels of arousal (sleep deprivation or caffeine administration), concluding that the thalamus is involved in mediating the interaction of attention and arousal. Bendlin and colleagues found caffeine to stabilize the extent of neuronal activation in repetitive word stem completion, counteracting the general task practice effect. Recently, Koppelstaetter and colleagues assessed the effect of caffeine on verbal working memory demonstrating a modulatory effect of caffeine on brain regions (medial frontopolar and anterior cingulate cortex) that have been associated with attentional and executive functions. This review surveys and discusses neuroimaging findings on 1) how caffeine affects the contrast underlying fMRI techniques, particularly the blood oxygen level dependent contrast (BOLD fMRI), and 2) how caffeine operates on neuronal activity underlying cognition, to understand the effect of caffeine on behavior and its neurobiological underpinnings.

Keywords: Caffeine, functional magnetic resonance imaging (fMRI), higher cognitive functions, working memory

HISTORY, METABOLISM, AND BASIC MECHANISMS OF ACTION OF CAFFEINE IN THE BRAIN

Caffeine-containing foods and beverages have been consumed since ancient times but coffee was introduced to the Western world only a few hundred years ago. Presently, caffeine is the most popular behaviorally active substance worldwide. Caffeine is consumed mainly in the form of coffee, tea or soft drinks, although

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it is found in a variety of foods and beverages. Depending on the type and preparation, a cup of coffee contains between 19 and 177 mg of caffeine. The mean daily caffeine consumption per person varies, depending on culture and geographical position, reaching from approximately 170 to 210 mg/d in the United States, UK and Canada to 410 mg/d in Scandinavia. Neither acute nor chronic consumption (within usual limits) appear to have relevant negative consequences on health. Ordinary caffeine use is generally not considered to be a case of drug abuse.

Caffeine is absorbed rapidly from the gastrointestinal tract and is nearly 100% bioavailable. Peak plasma caffeine concentration is reached between 15 to 120 min after oral ingestion and plasma half-life ranges between 3 to 8 hours. However, its absorption is incomplete when ingested in the form of coffee. Due to its hydrophobic properties caffeine readily crosses the blood-brain barrier. Following peak absorption, brain levels remain stable for at least one hour [1,2]. Caffeine is metabolized by the liver; some metabolites also possess marked pharmacological activity.

Caffeine exerts its action mainly through a nonselective antagonism of cerebral adenosine A_1 and A_2 receptors [3], although there are important secondary effects on several classes of neurotransmitters, e.g., noradrenaline, dopamine, and acetylcholine. Since adenosine receptors display a general inhibitory effect on neural activity [4], a receptor antagonist has stimulant properties through disinhibitory mechanisms [3, 4]. However, caffeine acts not only as an excitatory neurostimulant but also as a vasoconstrictor causing reduction in cerebral blood flow (CBF) [3]. Because increased neuronal activity is thought to be exerted mainly through action on A_1 receptors, whereas vasoconstriction is mediated mainly through action on A_2 receptors, a nonselective antagonist can have both neural and vascular effects depending on the ratio of A_1 to A_2 receptors in a given brain region [5]. Hence, caffeine affects the brain by a localized combination of neural and vascular responses [5].

Caffeine is used mainly because of perceived stimulant properties. Caffeine is generally thought to provide benefits such as enhanced mental alertness, energy, and a sense of well-being. Various psychopharmacological studies investigated the different effects that caffeine exerts on behavior. Caffeine was found to possess beneficial effects on psychomotor function, vigilance, and mood. Furthermore, caffeine could enhance learning and memory. Yet the aforementioned benefits could not always be unequivocally demonstrated in studies, and observed effects sometimes tended to be small. Nevertheless, caffeine has been found to enhance task performance through increase of a) cortical activation, b) the rate at which information about a stimulus accumulates, c) selectivity to further processing of the primary attribute, and d) speed of motor processes via central or peripheral mechanisms [6]. It is not clear yet whether the observed beneficial effects on learning, memory, and performance derive from a direct enhancement of specific cognitive functions or can be attributed to increasing of arousal and overcoming fatigue [7–10].

COGNITIVE FUNCTIONS

Cognitive abilities are often characterized by their complexity and the number of cognitive processes they rely on as more fundamental simple “low” order brain functions, as distinct from computationally more demanding and complex “high” order brain functions. Functions like those involved in early perception and motor control usually are considered to belong to the “lower” category [11]. Higher functions most commonly refer to mental operations that are used in novel situations where no well-established stimulus-response association is existent or when errors/suboptimal outcomes are detected during “standard” behavior. As such, reasoning, problem solving, and decision-making rank among the “higher” functions. According to most theories, higher cognitive function entails the modulation of lower-level processes depending on abstract goals and intentions, by factors such as selective attention [12]. This modulation permits adaptation to novel or changing situations. However, in the early analysis of perceptual inputs, adaptive responses in terms of decreased reactions to non-novel stimuli (“response suppression”) can occur. The higher cognitive processes that enable an individual to plan, sequence, initiate, and sustain behavior towards a goal, including self-monitoring and adaptive responding, are summarized as executive functions. Most of these functions are mediated by the frontal lobes (and to some extent by the parietal lobes) [13–15]. At the core of many simple, as well as high order cognitive functions, lie memory processes. Memory processes can be categorized with respect to both contents and time. In the time domain, short-term memory can be distinguished from long-term memory based on the persistence of memory traces [16]: short-term or working memory temporarily retains a limited amount of information in a highly accessible form. Without rehearsal, information is

available in working memory for only a certain duration ranging from several seconds to as long as a minute. Different schemes of working memory have been proposed with the tripartite multi-component model introduced by Baddeley and Hitch being widely accepted: working memory consists of three components, short-term storages of information that are domain-specific (verbal phonological loop and visuo-spatial sketchpad) and a panmodal central executive that operates on the contents of this storage [17]. The central executive may either be a unitary system or multiple systems of varying functions including attentional control, selection, inhibition, and the updating, maintenance, and integration of information from the two supplying subsystems. The central executive of working memory and the executive functions are somehow overlapping concepts and share many cortical representations [13]. The neural basis of both is a network of brain areas in the frontal and parietal lobes [16,18,19].

NEUROIMAGING WITH FUNCTIONAL MRI

Functional brain imaging with MR (fMRI) allows inferences to be made about cerebral activity underlying cognition. However, fMRI does not directly measure neuronal activity but measures the hemodynamic sequelae of cerebral activation. The two fMRI techniques mostly employed are: 1) The direct measurement of the cerebral blood flow (perfusion MRI) and 2) the measurement of temporal changes of regional cerebrovascular blood oxygenation caused by local differences in cerebral blood flow (blood oxygenation level dependent (BOLD) contrast imaging).

Physiological basis

Local brain activity exerts a regional increase in oxygen and glucose metabolism. To meet the metabolic demands, the local response is an increase in regional blood flow (rCBF) to regions of increased neural activity. Neuronal activity can elicit rCBF changes in the magnitude of about ten to twenty percent. Thus, neuronal activity can be indirectly measured and localised by measuring this hemodynamic response (HRF). Although regional glucose metabolism and rCBF are intensely increased during cerebral activity, the oxygen metabolism is not increased in direct proportion [20]. The abundant inflow of oxygenated blood thus more than compensates for any increase in oxygen consumption and extraction and causes a dilution of the deoxygenated blood in the draining vessels (i.e., the oxygen extraction fraction declines). Thus, the hemodynamic response (HRF) leads to regional changes in the relative concentration of oxyhemoglobin and deoxyhemoglobin, favoring the former. Nevertheless, the specific mechanisms of the coupling between neuronal activity, oxidative as well as glucose metabolism, and rCBF remain unclear [21]. Vasoactive substances, nitric oxide, neurotransmitters, and biomechanical factors have been postulated to mediate the connection between neuronal activation and rCBF response [22]. In addition to these local factors the rCBF response may depend on global perfusion regulation. Yet, many inconsistent results on the dependence of local activation related BOLD signal changes on the baseline BOLD signal have been reported. The effect of global cerebrovascular modulation (vasoconstriction or vasodilatation) on the local activation-induced BOLD response was either up- or down-regulating, depending on the experimental setting [22]. Two alternative models have emerged: The first model states that local CBF changes induced by stimulation are independent of and additive to the global CBF, i.e. the absolute increase in rCBF remains constant whereas the relative changes vary. Vice versa, the other model states that local changes depend on and are proportional to the global CBF such that the relative local changes remain constant whereas the absolute increase in rCBF varies [23].

Due to the complexity of the field, different methodological approaches to measurement of the hemodynamic response to cerebral activation were attempted in the last few years.

BOLD contrast imaging

Deoxygenated and oxygenated hemoglobin possess different magnetization properties: the presence of deoxygenated blood decreases the MR signal in specially weighted sequences; vice versa the signal increases with decreasing deoxyhemoglobin concentration. Thus, hemoglobin can act as an endogenous contrast agent in neuroimaging. This technique is known as blood oxygenation level dependent (BOLD) contrast imaging. The BOLD signal is a complex function of regional dynamic changes in CBF, cerebral blood volume (CBV), and the cerebral metabolic rate of oxygen ($CMRO_2$) [24]. The exact model relating the BOLD signal to blood flow and oxygen supply is still under debate. Nonetheless, the course of the BOLD signal closely resembles the cerebral HRF. With high-field MR scanners ($\geqslant 4$ T) a small decrease preceding the in-

crease in BOLD signal can be detected, called the initial dip. It is hypothesized to represent the initial increase in deoxygenated blood before the dilution caused by the increased regional blood flow sets in. The initial dip may be more spatially specific to the neuronal activation than the following positive response of the BOLD signal [25]. However, it seems not to be the neuronal output in terms of action potentials that is captured by fMRI measurements, but the overall post-synaptic activity of a relatively large assembly of neurons (i.e., the local field potentials) [26]. Thus, regional cerebral activation, as seen by fMRI, predominantly reflects input to that area and the corresponding changes in information processing [20].

BOLD signal differences are small, usually in the range of one to three percent (1.5 T MR scanner). The MR sequence most commonly used for BOLD contrast imaging is echo-planar imaging (EPI).

Perfusion MR

"Arterial spin labeling" (ASL) leverages the magnetic properties of arterial water to use it as an endogenous blood flow tracer. Existing techniques fall into two categories depending on how the spin labeling is applied: pulsed techniques and continuous techniques [27]. Despite sharing a similar basis, each approach has its own advantages and limitations that affect its ability to quantify perfusion. In both cases protons of arterial blood are exited ("tagged" or "labeled") by radio-frequency (RF) magnetization inversion upstream of a slice of interest. The labeled blood subsequently arrives in the slice of interest, where arterial water mixes with tissue water and thereby alters the tissue magnetization. An image is acquired, which shows changes in intensity in proportion to the rCBF to that slice. It is possible to obtain a measurement of rCBF by subtracting the image in which inflowing blood was labeled from a control image in which no inversion tag is applied. Quantitative perfusion maps can be calculated if other parameters (e.g., tissue T1, efficiency of spin labeling) are measured as well. Labeling may be performed either with the imaging coil or with an additional separate RF coil. Due to limitations in acquisition speed ASL measurements are usually not suited for fast event related designs. Moreover, ASL is limited in the number of slices to reasonably be acquired. However, as ASL measures the amount of arterial blood that has been delivered to the capillary beds, the signal may be more localized to the sites of neuronal activation than is the more postcapillary BOLD signal [27]. Recently, both imaging approaches (ASL and BOLD contrast) were used in combination.

FUNCTIONAL IMAGING OF HIGHER COGNITIVE FUNCTIONS

Much of what is known about the localization of cognitive functions within the living human brain before fMRI techniques entered the field stemmed from positron emission tomography (PET). Yet, the advent of event-related fMRI provided a higher degree of experimental control and inference [28]. While many findings from functional imaging confirmed what had been deduced from lesion studies, numerous regions being engaged in cognition could only be identified by means of neuroimaging. The frontal lobes were already known to be critically involved in higher cognition due to the extensive literature on lesions studies. Yet, neuroimaging could demonstrate the convergence of functional integration and functional specialization within the frontal lobes in higher cognitive functions [28,29]. With fMRI, processing of planning and problem solving could be localized to distinct prefrontal cortical areas [30]. Although the importance of the frontal lobes in executive functions was evidenced in lesion studies (for a review see [31]), component processes of the executive functions could be mapped to specific parts of the frontal and parietal lobes with neuroimaging [32]. Executive functioning relies on the flexible workspace of working memory: the manipulation and continuous adjustment of its contents based on newer incoming external (sensory input) and internal information (retrieval from long-term memory) are essential to facilitate adaptive responding to novel or complex situations. Thus, executive functions and working memory are heavily interwoven and share many cortical representations [13]. Numerous neuroimaging studies using PET and fMRI have consistently demonstrated the involvement of a bilateral fronto-parietal network, including the anterior cingulate cortex (ACC), and the cuneus and precuneus in working memory [16,18,19]. Distinct cortical areas have been associated with specific components of working memory. Processes of central executive functions like attention, inhibition, monitoring, planning, and task management have been localized in the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC), and in the ACC, whereas the temporary storage of information is supposed to be mediated by the parietal cortices [18]. A well-investigated working memory task aiming both at the executive function of updating and on the phonological loop is the verbal n-back task [16]: letters are presented in rapid succession and the subjects have to decide whether the actual letter is identical to the

one presented n items previously (e.g., 1-, 2-, 3-back task). In an fMRI study Hautzel and colleagues found a widespread fronto-parietal network, including the ACC and the cerebellum [33]. Lately, the same group investigated the cognitive involvement of the cerebellum in working memory executive functions [34].

More recently, functional brain imaging with MRI (fMRI) entered the field of neuropharmacology to explore the sites and mechanisms of action of various pharmacological agents within the performing brain.

PHARMACOLOGICAL fMRI

Through pharmacological intervention studies substantial progress has been made in fractionating different components of cognition and in elucidating the underlying neurochemical and neural substrates of these processes [35]. A large body of literature covers pharmacological interventions to elucidate the underpinnings of memory processes, especially of working memory [36]. While fMRI techniques have long been used to study sensory, motor, and cognitive functions, the imaging of drug action in the brain and of the consequences on brain function and cognitive processes has been the field of positron emission tomography (PET). However, due to the higher temporal and spatial resolution of fMRI and the absence of ionizing radiation, there has been growing interest in using this technique to map the modulatory effects of administered pharmacological agents on regional brain activity. Because the impetus of fMRI on pharmacological research has been realized, pharmacological fMRI is increasingly used to explore the sites and mechanisms of action of different neuropharmaceuticals on cognition [37–40].

Due to their eminent role in cognition, the executive functions and working memory have been a target of pharmacological intervention. A key player in these functions are the frontal lobes, which receive ascending input from various neuromodulatory systems [35]. In particular, monoaminergic (e.g., dopaminergic, noradrenergic) modulation was shown to affect executive and working memory processes [41]. Mehta et al. could demonstrate beneficial effects of methylphenidate (a reuptake inhibitor of dopamine and noradrenaline) on a spatial working memory test by modulating regions in the dorsolateral, prefrontal, and posterior parietal cortex [42]. More complex effects could be demonstrated by direct interaction with dopamine receptors: examining the influence of bromocriptine (a dopamine D_2 receptor agonist) on executive function and working memory tasks, Kimberg and colleagues could demonstrate task-related decrease in cortical activity mainly in parietal areas without altering working memory performance [43]. In an fMRI study Gibbs and D'Esposito also investigated the effects of bromocriptine on working memory [44]. Dopaminergic manipulation was associated with reduced brain activation during encoding in parietal areas, but an increased activity during recall/recognition in frontal and parietal areas [44].

However, because pharmacological agents may interfere with the mechanisms responsible for the functional contrast underlying fMRI, such experiments should be carefully designed and analyzed [45]. Specifically, introducing a drug into the system could potentially alter the coupling of neural activity with regional cerebral blood flow and/or the extraction of oxygen from blood, or may cause local or global cardiovascular changes unrelated to neural activity [38].

Despite the common use of caffeine and the probable presence of its actions in the subjects of neuroimaging studies, only a limited number of neuroimaging studies dealt with its effect on the physiological mechanisms that give rise to the fMRI signal (e.g., the BOLD contrast). Even fewer neuroimaging studies examined the effects that caffeine exerts on cognition.

IMAGING THE CEREBRAL EFFECTS OF CAFFEINE: METHODOLOGICAL AND PHYSIOLOGICAL CONSIDERATIONS

It is not by chance that caffeine is the stimulant drug of choice to a vast number of people. Psychopharmacological studies have demonstrated its beneficial effects on psychomotor function, learning and memory. Cognitive pharmacology could disentangle neurotransmitters involved in these functions and how caffeine affects them. But where does caffeine action on cognitive functioning take place in the brain? Functional imaging offers the unprecedented opportunity to explore the sites and mechanisms of action of caffeine in the performing brain. However, functional imaging techniques do not directly capture neuronal activity, but rely on the coupling of the hemodynamic response to neuronal activation and metabolism. Yet, caffeine affects the brain by a localized combination of neural and vascular responses [5], and may interfere with the very mechanisms responsible for the functional contrast underlying functional imaging. Hence, it is important to identify the basic effects of caffeine on the CBF and the BOLD signal both at rest and under stimulation to

assess its effect on cognition. Much effort has been made to elucidate the effect of caffeine on measures in fMRI. In brief, the results from previous research are complex and sometimes confusing. This may be on the one hand due to inter-subject variability in the metabolism of caffeine, and formation of tolerance depending on individual caffeine consumption [46]. On the other hand, it may depend on the complex nature of the neurovascular coupling itself, which is not yet fully understood.

Thus, the following issues have to be resolved in imaging the cerebral effects of caffeine: How does caffeine affect 1) baseline CBF and BOLD signal, 2) the magnitude, and 3) the temporal dynamics and shape of the rCBF and BOLD response to cerebral activation?

Effects of caffeine on baseline CBF and BOLD signal and on the magnitude of the rCBF and BOLD response to cerebral activation

As caffeine exerts its action through nonselective antagonism of both adenosine A_1 (neuroexcitatory effects) and A_2 (vasoconstrictive effects) receptors, caffeine will directly affect CBF. With PET a decrease in the resting-state CBF by as much as 20 to 30% could be demonstrated following doses of 200 mg caffeine (equivalent of 2 to 3 cups of coffee) [47]. This decrease in baseline CBF and its degree could be confirmed in most of the studies accomplished with perfusion MRI. However, the consequences to baseline BOLD signal and to the magnitude of the rCBF and BOLD response to neuronal activation are less clear.

Mulderink and colleagues investigated the effects of caffeine on resting perfusion and visually cued complex finger motor task activation in an initial fMRI study [48]. Resting perfusion was measured with an ASL sequence. They reported a decrease in the average baseline perfusion level of about 11 to 13%. The researchers suggested that the reduction in CBF will affect the BOLD signal baseline in the same way but supplied no direct measure of the BOLD signal baseline. As subsequent BOLD activation changes are measured from this signal baseline, the lowered baseline is assumed to provide a greater range for the BOLD signal during activation. In consequence, the BOLD response is expected to be measurably larger. The authors concluded that caffeine serves as a "contrast booster" for fMRI experiments. Laurienti and colleagues could confirm the reductive effect of caffeine on resting-state CBF with an ASL technique. However, they could not consistently enhance BOLD response intensity magnitude to visual and auditory stimulation by simply decreasing resting perfusion: half of the study population showed decreases and half showed increases in BOLD signal intensity magnitude [5]. Yet again, no direct measure of BOLD signal baseline was reported. Laurienti et al. concluded that the relationship between resting cerebral perfusion and the magnitude of BOLD signal intensity is already complex, and proposed that any drug or condition that has both vascular and neural effects will result in an even more complex relationship between resting cerebral perfusion and BOLD signal intensity changes. Thus, the magnitude of the BOLD signal can increase or decrease due to caffeine, by a combination of effects on the vascular and neural level, which depend on many factors, such as receptor number and affinity [5]. Changes in receptor expression and affinity are a component of the formation of drug tolerance, which depends on individual caffeine intake. In another study, Laurienti and coworkers took a closer look at the possible interaction of regular caffeine consumption and the magnitude of the BOLD response to visual and auditory stimulation. They could demonstrate that the BOLD response was boosted for high caffeine users under visual stimulation (with an upward trend under auditory simulation), but tended to decrease BOLD response in low-users. They proposed a differential expression of A_1 and A_2 receptors due to habitually high caffeine ingestion that leads to a differential weighting of the A_1 and A_2 receptor mediated effects in the two study populations [49]. Field et al. investigated this differential effect of caffeine in the brains of subjects accustomed to high doses of caffeine in comparison to those who are not in a quantitative MR perfusion study [50]. They found high caffeine users in the withdrawal state to possess a significantly higher baseline CBF than low caffeine users. After administration of caffeine both high and low users experienced a reduction in CBF (19 to 26%). Yet these reductions seemed systematic: high caffeine users experienced a reduction of CBF following administration of caffeine to the level of abstained low caffeine users. Low caffeine users experienced a reduction of CBF after administration of caffeine further below the level of high caffeine users under the influence of caffeine. These results suggest a full drug tolerance of the high caffeine users. However, the picture becomes less clear after a recent study of Addicott and colleagues employing a larger sample of participants and a more thorough methodology [46]. Applying a tripartite grouping of low, moderate, and high caffeine users, the participants received caffeine both after withdrawal and under reg-

ular caffeine drinking habits. Moderate and high caffeine users had similarly greater CBF than low users in the abstained state, but high caffeine users receiving caffeine showed less CBF than abstained low caffeine users. Without caffeine withdrawal (i.e. on regular caffeine drinking habits) the high users had a trend towards less CBF than the low and moderate users. Addicott et al. suggest a limited ability of the cerebrovascular adenosine system to compensate for high amounts of daily caffeine use. These inconsistencies raise the methodological issue of whether to instruct study participants to refrain from caffeine usage prior to fMRI, although this may result in abnormally high CBF due to caffeine withdrawal, or to instruct them to continue their normal caffeine use.

So far, the presented studies could demonstrate unequivocally only the reductive effect of caffeine on CBF. The effect of caffeine to baseline BOLD signal and to the magnitude of the rCBF and BOLD response to neuronal activation are less clear. This may be due to the combination of neurostimulant (most likely increasing neuronal metabolic demands) and vasoactive (reducing CBF) effects of caffeine. The complex relationship between CBF, oxygen metabolism and BOLD effect has been investigated by Perthen and colleagues using visual stimulation and a hypercapnia-calibrated BOLD methodology [51]. The calibrated BOLD approach uses ASL to establish a defined relationship between CBF, BOLD signal, and cerebral metabolic rate of oxygen ($CMRO_2$). For this purpose, the CBF and BOLD responses to mild hypercapnia, as well as task-induced activation, are measured. As hypercapnia increases CBF without eliciting changes in $CMRO_2$, it is used to calibrate the BOLD signal by quantifying the contribution of CBF changes to the BOLD response in the absence of $CMRO_2$ changes. A mathematical model is then used to combine the CBF and BOLD activation responses with the hypercapnia-calibrated relationship between BOLD and CBF to estimate the $CMRO_2$ change due to activation [51,52]. The coupling between changes in blood flow and oxygen metabolism can be described by the ratio of the fractional CBF change to the fractional $CMRO_2$ change. The calibrated BOLD approach is an excellent tool for studying the effects of substances such as caffeine on BOLD, as it can provide a measurement of the CBF:$CMRO_2$ coupling ratio, which is expected to change given the neurostimulative and vasoactive effects of caffeine [52]. Perthen and coworkers could demonstrate a lowering of the CBF and BOLD signal baseline following caffeine. As $CMRO_2$ remained constant despite the reduced CBF, the coupling ratio of $CMRO_2$ and CBF had changed. To satisfy the constant metabolic demands in the face of a reduced CBF, an increase in oxygen extraction fraction is to be expected. This increase in oxygen extraction most likely leads to an increase in deoxyhaemoglobin concentration, which diminishes the BOLD signal baseline. Unfortunately, Perthen et al. do not report on the effect of caffeine on rCBF or BOLD response to visual stimulation. However, another similar calibrated BOLD study published by Chen and Parrish examined how caffeine alters the coupling between CBF and $CMRO_2$ during a motor and visual task [52]: caffeine decreases baseline CBF but does not alter the percentage change in CBF to stimulation. In contrast, caffeine increases percentage change in BOLD response to motor and visual stimulation. Moreover, caffeine increases $CMRO_2$ under stimulation, possibly due to an increasing number of activated neurons [52]. Thus, caffeine decreases the coupling ratio of $CMRO_2$ and CBF. The same research group recently investigated the dose dependent effect of caffeine on activation-induced BOLD and CBF responses with a combined ASL/EPI (dual echo) technique. Three different doses of caffeine infusion were administered in a parametric design. Their results were partly conflicting, as both percentage change in CBF and percentage change in BOLD response increased under the influence of caffeine. The CBF response increased linearly with increasing doses of caffeine, whereas the BOLD response increased in non-linear fashion. Chen and colleagues assumed that this difference could be related to a different distribution of A_1 and A_2 receptors within the brain leading to a differential weighting in the vasoactive and neuroexcitatory effects of caffeine [53]. Thus, caffeine may boost the BOLD response but not in straightforward fashion. Moreover, they found an alteration of the temporal dynamic of the bold response in terms of a shortening of the BOLD response.

Effects of caffeine on the temporal dynamics and shape of the rCBF and BOLD response to cerebral activation

The research group around Liu and Behzadi concentrated on the caffeine-induced effects on the visual BOLD response using a combined ASL/EPI (dual echo) imaging technique. They found an alteration of the temporal dynamics of the visual BOLD response in terms of a quickening and shortening of the BOLD response [54]. Moreover they found an increase in the percentage change in BOLD response to

stimulation. They also could demonstrate the caffeine-induced decrease in baseline CBF. They supposed that the caffeine-induced changes in BOLD signal are due primarily to this decrease in baseline CBF. They made reference to a biomechanical model proposed from Behzadi et al. linking rCBF response to biomechanical responsiveness of the arterioles, which in turn depends on the relative contributions of the vascular smooth muscle and connective tissue to the dynamics of the arteriolar wall [24,55]. According to the model, the vascular smooth muscle exerts more force in order to constrict the arteriole in response to vasoconstrictive agents, such as caffeine, whereas the force exerted by the connective tissue is reduced. This redistribution of forces makes the arteriole more responsive and speeds up the dynamic CBF response [55]. The venous compartment is treated as a distensible balloon [56]. The compliance model determines the flow into the balloon. The balloon model with viscoelastic terms is then used to model the dynamic relation between CBF, CBV, and $CMRO_2$, and to estimate the total volume of deoxyhemoglobin, which all determine the appearance of the BOLD signal. In a further study using a similar experiment protocol Behzadi and Liu found a caffeine-induced reduction of the so-called "initial dip" in the visual BOLD response [55]. Within the first few seconds following the onset of increased neuronal activity, the rate of oxygen metabolism ($CMRO_2$) increases faster than rCBF, leading to a transient increase in deoxyhemoglobin concentration that causes an initial decrease ("dip") in the BOLD signal [55]. Behzadi et al. argued that the disappearance of the initial dip is most likely due to a quickening of the CBF response as stated in the aforementioned arteriolar compliance model. However, as caffeine can reduce the signal-to-noise-ratio and contrast-to-noise-ratio in fMRI measurements [57], these effects may have disguised the initial dip. Moreover they found a decrease in the baseline CBF and an increase in the percentage change in BOLD response to stimulation. Two studies from the same research group are at variance with the aforementioned studies with regard to the arteriolar compliance model: Rack-Gomer et al. investigated the effect of caffeine on resting state connectivity in the motor cortex under the influence of caffeine using the combined ASL/EPI (dual echo) imaging technique. As their prior work with task-related BOLD fMRI suggested that caffeine may increase the sensitivity of the BOLD signal to stimulated neural activity, they hypothesized that caffeine would also increase the sensitivity of BOLD fluctuations to spontaneous neural activity and thus increase resting-state BOLD connectivity. Although they could demonstrate a decrease of CBF baseline following caffeine ingestion and replicated that the caffeine-induced reduction in CBF was associated with an acceleration of the BOLD response to a finger-tapping task, they found caffeine to reduce resting-state BOLD functional connectivity in the motor cortex. As both spectral amplitude of low-frequency BOLD fluctuations and the coherence between resting BOLD fluctuations were diminished, an increase in biomechanical responsiveness was not a dominant factor of this effect. Irrespective of the causation, a reduced motor functional connectivity raises the impression of deterioration in motor function. Yet, a beneficial impact on psychomotor function is among the most reliably demonstrated effects of caffeine. The authors suggested that the rather high dose of caffeine in the study resulted in a counterproductive effect on motor learning. In 2008 the group compared pre- and postcaffeine functional maps of visual CBF and BOLD response in a hypercapnia-calibrated BOLD approach (this study is part of the aforementioned study of Perthen et al. [51]). They demonstrated a significant decrease of the number of functionally active voxels in the CBF maps but not the BOLD maps [57]. Caffeine significantly decreased the CBF baseline and absolute CBF response to stimulation but increased the percentage CBF change to a combined visual and motor task, which is inconsistent to the additive and the proportional model of the dependence of the functional CBF response on baseline CBF. Caffeine did not accelerate the temporal dynamics of the CBF response, whereas it accelerates the temporal dynamics of the BOLD response. Caffeine decreases the BOLD signal baseline but did not affect absolute or percentage change in BOLD response to stimulation. These somehow conflicting results may reflect the different physiological origins of the two responses, while the CBF response reflects the change in a single physiological variable, the BOLD response exhibits a complex dependence on changes in cerebral blood flow, cerebral blood volume and oxygen metabolism [57].

Although the results are complex and sometimes conflicting, some conclusions can be drawn: caffeine reduces the baseline CBF and seems to reduce the baseline BOLD signal. In people habitually consuming caffeine the impact is dependent on a combination of drug tolerance to caffeine and withdrawal effects. Caffeine alters neurovascular coupling and affects the amplitude of the rCBF and BOLD response to neuronal activation, again depending on both drug tolerance to caffeine and withdrawal effects. Predominantly there is

an increase in the BOLD response. Caffeine alters the temporal dynamics of the BOLD response in terms of a quickening and shortening. However, caffeine may not affect the temporal dynamics of the CBF response in the same way.

So far, it is not clear whether these vascular effects contribute to the impact of caffeine on brain function or are just epiphenomenal.

IMAGING THE EFFECTS OF CAFFEINE ON COGNITION

Only a few fMRI studies investigated the effects of caffeine on cognitive functions other than the aforementioned comparatively simple perceptual or motor tasks [58–60].

In 1998 Portas and colleagues investigated brain activity with fMRI in an attentional task (passive viewing of a checkerboard, active responding to a visually presented target) under different levels of arousal achieved through sleep deprivation or caffeine administration [60]. Activity evoked in the ventrolateral thalamus by the task changed as a function of arousal, with highest levels of attention-related thalamic activity seen in states of low arousal (after sleep deprivation) compared with those of normal or high arousal (after caffeine ingestion). They concluded that the thalamus is involved in mediating the interaction of attention and arousal. Although they could demonstrate activation of the cortical attentional frontoparietal network, they could not show consistent changes in cortical activity during low or high (after caffeine ingestion) arousal across subjects. However, there was also no consistent effect of the different levels of arousal on cortical activity under simple visual stimulation. Unfortunately, Portas et al. did not report whether differences in cortical activation have been observed solely between the high arousal (after caffeine ingestion) and the normal arousal condition. In respect of behavioral data, the attentional task performance did not show a significant change during different levels of arousal. They argued that specific changes in performance are only seen for longer and more demanding tasks after sleep deprivation [60].

Bendlin and colleagues used a word stem completion (WSC) task in a perfusion and BOLD contrast fMRI experiment to investigate the effects of caffeine on the general task practice effect [58]. Several methodological issues were also considered concerning the influence of caffeine on CBF and BOLD baseline signal and BOLD response. WSC tasks show significant stimulus repetition effects over time that result in a decrease in BOLD signal amplitude in multiple brain regions including frontoparietal areas [61–64]. Bendlin et al. could demonstrate that caffeine stabilizes the extent of neuronal activation in tasks, counteracting the general task practice effect, presumably due to the action of caffeine on sustained alertness and attention. However, as the modulation of the hemodynamic response in repetitive task is often considered a “fine tuning”, this finding seems somehow unexpected. On the physiological level they could demonstrate a reduction of baseline CBF following caffeine ingestion. Yet, in contrast to most of the studies mentioned in the preceding section, they found no effect of caffeine on the baseline BOLD signal, or on BOLD response amplitude.

To our knowledge, there is only one fMRI study which investigated the effect of caffeine on neuronal activity during higher cognition in terms of a verbal working memory task [59] (v. Fig. 1). In this study by Koppelstaetter and colleagues, 15 participants (abstained from caffeine and nicotine intake by a minimum of 12 hours) underwent two fMRI scan sessions on two different days (v. Fig. 2). They received an oral dose of either caffeine (100 mg) or placebo in crossover fashion and pseudo-randomized order. This moderate caffeine dosage was chosen to reflect caffeine intake of common drinking habits and to avoid physiological side-effects that might be noticed by the volunteers. Subjects had to perform a 2-back verbal working memory task in a conventional block design. Additionally, behavioral performance (percentage of correct responses (accuracy) and time (in ms) taken to respond (reaction time)) as well as physiological parameters (heart rate, systolic and diastolic blood pressure, mean arterial pressure, pulse oxymetry) were recorded.

They hypothesized that caffeine might selectively modulate the fMRI signal in frontal cortical brain areas, since the beneficial effects of caffeine on mental performance seem to be related to attention and executive functioning. An interaction analysis (task x pharmacointervention) of cortical activation under working memory demands within the caffeine and placebo condition revealed a distinct caffeine-related effect on the bilateral medial frontopolar cortex (BA 10), extending to the right anterior cingulate (BA 32) (v. Fig. 3). These brain areas are related to cognitive processes involved in working memory that have been associated with attentional and executive functions in terms of motivated attention, allocation of attention and error detection [65, 66], as well as planning, monitoring and problem solv-

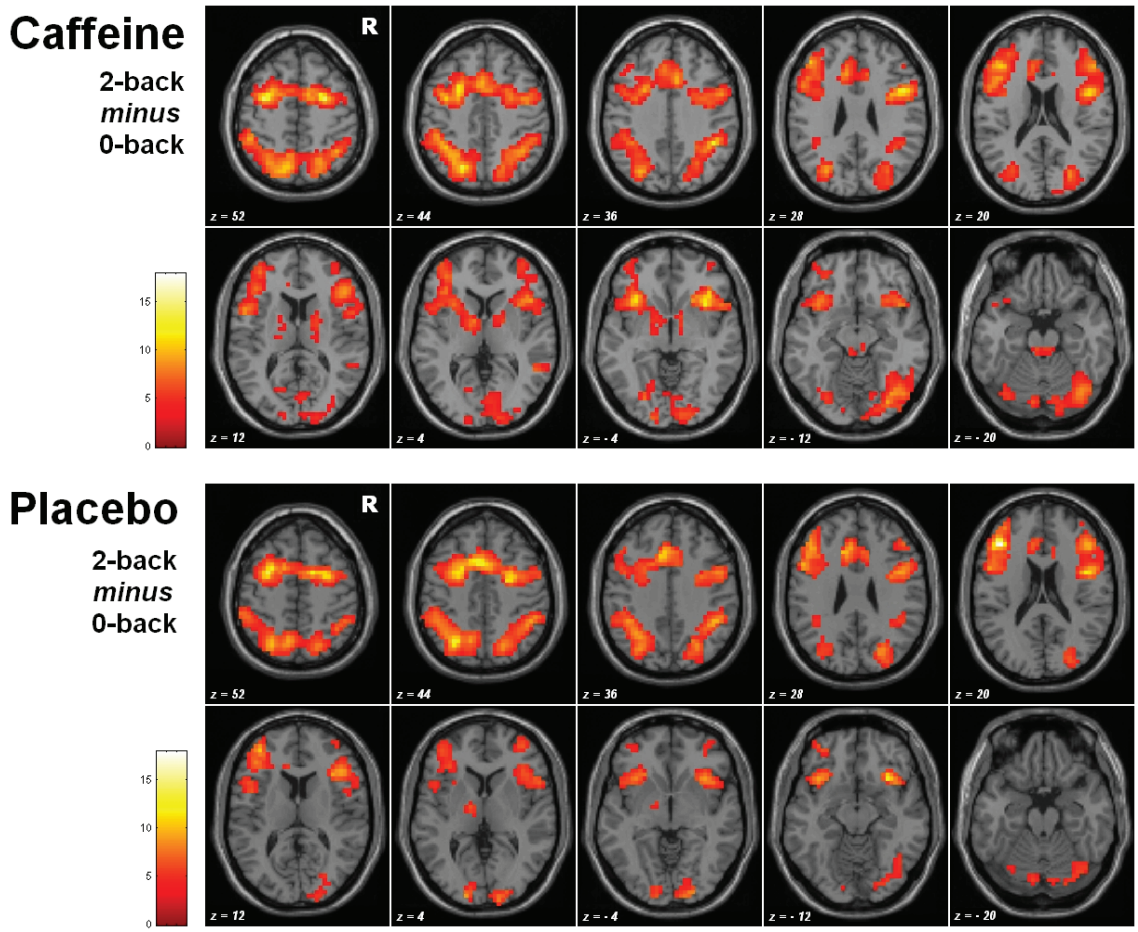

Fig. 1. Frontoparietal network of cortical activation found in the working memory task (SPM 2nd level subtraction analysis of the working memory and the reference conditions across both the caffeine and placebo groups superimposed on the canonical SPM2 T1 image. Activations were reported for clusters which surpassed an initial uncorrected threshold of $p < 0.001$ and had a corrected p-value of $p < 0.05$ on cluster level).

ing [67–69]. The regional specificity of the observed effect renders an explanation solely by a vascular effect unlikely, since the prefrontal or frontal cortex do not display a specifically high concentration of adenosine A_2 receptors [70], which are mainly responsible for vasoconstrictive effects of caffeine. Moreover, A_1 receptors, which mediate the neuroexcitatory effect of caffeine, are distributed differentially throughout the brain. As evidenced from both *in vitro* [71,72] and from combined *in vitro*/*in vivo* studies in humans [73], there are a significant amount of A_1 receptors in the basal ganglia and in neocortical regions, with the fourth highest density being localized in the frontal cortex. Thus, the differential distribution of A_1 receptors makes some cortical and subcortical regions more likely to be affected by caffeine than others. Since the effects of caffeine on the brain are mediated by a combination of neural and vascular responses [5], the researchers hypothesized that the observed modulation is mediated mainly by the neuroexcitatory action of caffeine on the specific brain regions that are involved in executive and attentional functions, rather than a general effect due to the influence of caffeine on the vasculature [59]. Apart from its action on adenosine receptors, caffeine exerts important secondary effects on several other neurotransmitter systems in different parts of the nervous system, e.g., noradrenergic, dopaminergic, and cholinergic transmission [3]. The prefrontal cortex is critically involved in cognition and receives ascending input from various neuromodulatory systems such as the dopaminergic system [35]. Pathologic disruption of these systems can lead to profound cognitive deficits. Parkinson's disease is a model for abnormal dopaminergic neuromodulation beyond motor functions, resulting in cognitive deficits including both low and high level processes [74,75]. The same systems that show sensi-

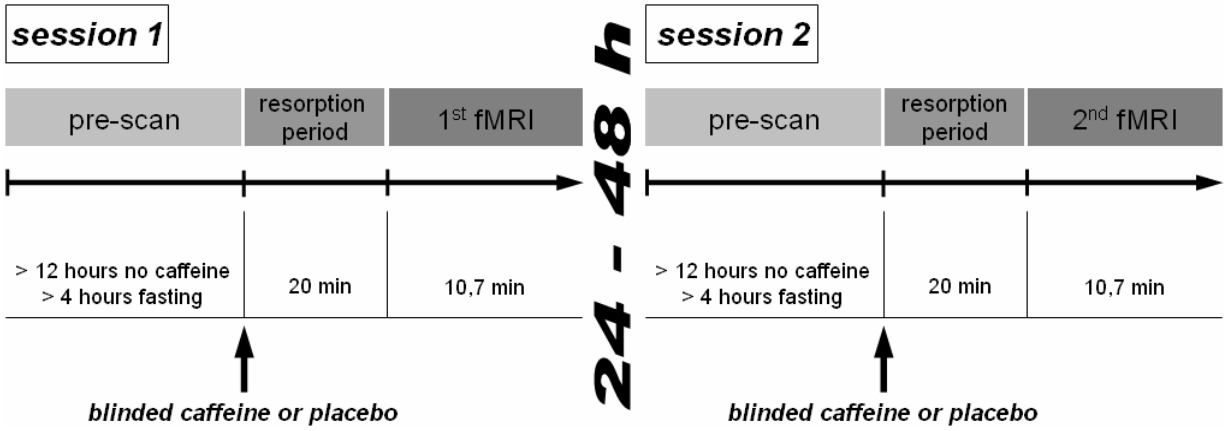

Fig. 2. Experimental design. Each subject underwent two fMRI scan sessions on two different days separated by a 24 to 48 hours interval. Subjects abstained from caffeine and nicotine intake by a minimum of 12 hours and fasted for at least 4 hours prior to each scan session. Subjects received an oral dose of either caffeine (100 mg) or placebo in crossover fashion and pseudo-randomized order 20 min prior to the individual fMRI scan sessions.

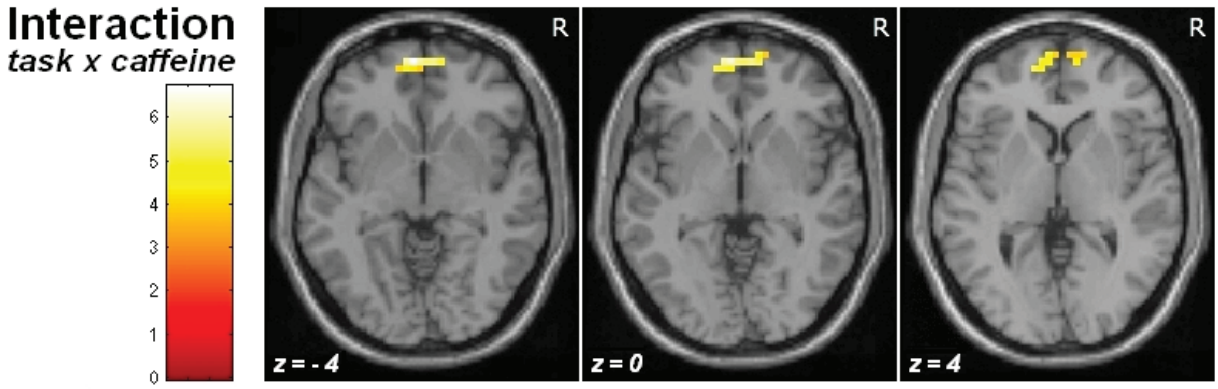

Fig. 3. Modulating effect of caffeine on neuronal activation in the medial frontopolar cortex in the working memory task (SPM 2nd level interaction analysis superimposed on the canonical SPM2 T1 image. Activations were reported for clusters which surpassed an initial uncorrected threshold of $p < 0.001$ and had a corrected p-value of $p < 0.05$ on cluster level).

tivity to pathological dopaminergic modulation are also affected by caffeine. This might also generalize to other neurotransmitter systems. This strengthens the assumption that the observed effect of caffeine within the frontal cortex was of a neuromodulatory sort. In contrast to several other psychopharmacological studies [7, 8,10,76], no significant caffeine-related behavioral effects were observed. The researchers argued that this difference could be due to the rather low dosage of caffeine used in this study, which was chosen to avoid physiological side effects noticeable to the volunteers, as well as to reflect caffeine intake of common drinking habits. Moreover, the authors concluded that the absence of significant behavioral effects held the advantage that the neuroimaging results were likely to reflect specific actions of caffeine and cannot be alternatively explained by task difficulty effects and differences in task performance.

CONCLUSION – PERSPECTIVE

Caffeine affects the brain by a localized combination of neural and vascular effects as it is both a neurostimulant and a vasoconstrictor. Due to the vasoactive effect, caffeine reduces resting CBF and alters the neurovascular coupling. However, it is not clear whether the vascular effects contribute to the impact of caffeine on brain function or are just epiphenomenal. Yet they have important consequences on studying brain function with fMRI BOLD contrast.

So far, only a few fMRI studies have investigated the effects of caffeine on cognitive functions other than comparatively simple perceptual or motor tasks. Hence, there is no general model of the relation between caffeine and higher cognitive brain functions as evidenced with fMRI. Nonetheless, results from a word stem completion task demonstrated that caffeine stabilizes the extent of neuronal activation in repetitive tasks, counteracting the general task practice effect [58]. A first probable explanation of the effects of caffeine on higher cognitive brain functions was recently provided; a modulatory effect of caffeine on the specific brain regions involved in executive and attentional functions could be demonstrated in working memory [59].

Thus, from its introduction as a simple BOLD-booster to its role in the characterization of the relationship between local BOLD response and the prevailing cerebral blood flow level, caffeine is now beginning to reveal its action on cognitive functioning.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=216).

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