**The practicability of multimodal data fusion for simultaneous EEG-fMRI demonstrated on a cognitive control task**

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# **List of Abbreviations**

**ACC** anterior cingulate cortex

**AX-CPT** AX continuous performance task

**BOLD** blood oxygenation level dependent

**BCA** ballistocardiac artefact

**CPT** continuous performance task

**dACC** dorsal anterior cingulate cortex

**DDT** delay discounting task

**DLPFC** dorsolateral prefrontal cortex

**DMC** Dual Mechanisms of Cognitive Control

**DPX** Dot Pattern Expectancy

**ECG** electrocardiography

**EEG** electroencephalography

**ER** error rate

**ERP** event-related potential

**ERSP** event-related spectral perturbation

**fMRI** functional magnetic resonance imaging

**GA** gradient artefact

**GFP** global field power

**GLM** general linear model

**HRF** hemodynamic response function

**ICA** independent component analysis

**IFG** inferior frontal gyrus

**IIR** infinite impulse response

**jICA** joint independent component analysis

**LFP** local field potential

**MFG** middle frontal gyrus

**MUA** multi-unit cell activity

**N-PLS** multiway partial least squares

**PCA** principle component analysis

**PFC** prefrontal cortex

**pICA** parallel independent component analysis

**PSI** proactive behavioral shift index

**rDLPFC** rightdorsolateral prefrontal cortex

**RT** reaction time

**SMC** supplementary motor cortex

**sMRI** structural magnetic resonance imaging

**SVD** singular value decomposition

**WAIS-IV** Wechsler Intelligence Scale for Adults fourth edition

**WM** working memory

# **1. Theoretical Background and Aims**

## 1.1 The benefits of combining EEG and fMRI

Neuronal activity of cognitive or affective processes can be studied from a large variety of measures, thereby revealing unique perspectives on brain activation.

Electroencephalography (EEG) mainly reflects the summation of postsynaptic potentials in pyramid cells with a similar orientation at a cortical level (Luck, 2005). Through sufficient coverage of the head surface with electrodes, synchronized activity of these cells can be recorded at a high temporal resolution. Due to this capacity of observing changes on a scale of milliseconds, EEG is often chosen as a direct link to cortical activity. However, EEG is recorded at a relatively large distance from cells and considerable portions of the original activity spikes fall off outside a 50 µm radius (Henze, Borhegyi, & Csicsvari, 2000). In addition, shorter spike durations with high-frequency oscillations far above 200 Hz decrease the odds of spike summation. The measurement on the skull surface prevents higher frequency signals from affecting the EEG and the recorded signal predominantly consists of slower Local Field Potentials (LFP).

Unlike action potentials of single cells and multi-unit activity (MUA), LFP are bound to temporal and spatial summation. For this reason, EEG only represents the summation of surface potentials. Furthermore, despite advances in signal source estimation (e.g. Lei et al., 2011), its spatial resolution is severely limited. The inability to pinpoint neuronal sources and to reconstruct the original flow of current of a given potential on the head surface is in EEG literature referred to as the inverse problem (Koles, 1998; Christophe Phillips, Rugg, & Friston, 2002). Source estimation analyses, as a tool of uncovering dipoles and brain areas most likely responsible for event-related electric voltage fluctuation at the surface, rely on several assumptions. Among others these include largely homogenous electric conductivity and resistance throughout brain tissues, a linear mixing process of electric signals, a mathematical approximation of the orientation and fluctuation of the current as well as a fixed template for the anatomical brain structure underlying these approximations (Cuffin, 1998; Koles, 1998; Sanei, Chambers, Sanei, & Chambers, 2013; Xu, Xu, & He, 2004). Whereas the lack of knowledge on individual test subjects’ brain can be compensated by letting structural magnetic resonance imaging (sMRI) inform source estimations (Cristophe Phillips, Rugg, & Friston, 2002; Whittingstall, Bartels, Singh, Kwon, & Logothetis, 2010), other assumptions remain improbable to be met.

While the electromagnetic fields measured in the EEG directly relate to neuronal activity, MRI is taking advantage of differing magnetic properties of nuclei within tissues of the human brain to produce images of different spatial resolutions (Huettel, Song, & McCarthy, 2004). Functional magnetic resonance imaging (fMRI) for instance is based on blood oxygenation. Due to a powerful static magnetic field (), the magnetic moment of the atoms in the observed tissue adapts an orientation parallel or anti-parallel to the magnetic field. Through a high frequency coil placed above the subject, a controlled manipulation of the nuclei’s magnetic moments via radiofrequency pulses causes the nuclei’s spins to change their orientation. Superposed on the -field magnetic gradients fields form a new magnetic field and enable the successive acquisition of slices, which taken together form a 3D volume of the subject’s head. Relating the signal to a certain spatial point within a probe is a basic principle of most MRI techniques. In fMRI specifically the repeated assessment of haemoglobin in the brain and its location in the brain is used as an indicator of brain activation. The hemodynamics assessed by fMRI is linked to the oxygen consumption of neuron populations. Thus, fMRI results show the flow of oxygenated blood in accordance to the metabolic demands of brain regions (Logothetis & Wandell, 2004). For this reason, the signal used in fMRI contrasts is referred to as blood oxygenation level dependent (BOLD). With the idea in mind that brain regions supporting a cognitive process consume more oxygen, the BOLD is thought to vary in correspondence to increased synaptic current flow. Since the BOLD signal is a correlate of neuronal activity (Rosen, Buckner, & Dale, 1998), it is regarded as an indirect measure. Plus, it is confined to a low temporal resolution on a timescale of seconds. In return, functional BOLD contrasts offer a higher spatial resolution compared to other imaging methods, while still operating entirely non-invasively. As such, MRI is a powerful method for studying the spatial dynamics of brain activation and for gaining anatomical information without harming patients or test subjects.

Comparing the two methods, it becomes apparent that EEG and MRI complement each other well. Together they combine next to ideal temporal and spatial resolution (Debener, Ullsperger, Siegel, & Engel, 2006). Both measures require an in depth understanding about their signals’ physiological properties, in order to draw reasonable conclusions from experimental results. This is because their respective limitations often decrease the conclusions’ validity (Turner, Rodriguez, Norcia, McClure, & Steyvers, 2016). Instead of relying on a selective view with a single method, simultaneous or separate recordings provide multifaceted insights into brain activation. In principle, a setup for parallel EEG-fMRI experiments entails that subjects are tested at least twice using one test for each method separately (Herrmann & Debener, 2008). This type of experiment is easier to perform compared to concurrent recordings. More importantly, it ensures higher data quality, since EEG and MRI, in their basic configurations, inflict severe measurement artefacts on each other when combined (Allen, Josephs, & Turner, 2000; Bénar et al., 2003; Iannotti, Pittau, Michel, Vulliemoz, & Grouiller, 2014; Ihalainen et al., 2015). The two most impactful artefacts for the EEG are caused by the magnetic gradients during volume acquisition (i.e., gradient artefacts; Yan, Mullinger, Brookes, & Bowtell, 2009) and electromotive forces that are active as a result of moving electric charges within the magnetic field (i.e., ballistocardiac artefacts; Iannotti et al., 2014; Mullinger, Havenhand, & Bowtell, 2013).

Gradient artefacts (GA) are largely stationary and periodic changes in the EEG signal. They are most striking due to their high amplitude. Moreover, their characteristic shape and occurrence at a rate parallel to the repetition time (TR) set in the echo-planar imaging (EPI) sequence make them easy to spot. By contrast, ballistocardiac artefacts (BCA) arise from small movements of electric charges within the magnetic field (Mullinger, Havenhand, et al., 2013; Yan, Mullinger, Geirsdottir, & Bowtell, 2009). Most notable in terms of severity of EEG signal distortion are vibrations resulting from the MRI’s helium pump (Rothlübbers et al., 2015). These are handily prevented by temporarily turning off the helium pump during simultaneous data acquisition. Yet, smaller motions, such as subject movement, also account for BCA. Displacements of electrodes due to cerebral blood flow, head motion and muscle contraction pose a serious problem to the data quality. Due to its electrically conductive properties, even pulsatile blood flow in intracranial and large cranial arteries can account for this non-stationary, aperiodic and unobtrusive artefact group in the EEG.

Conversely, EEG-related artefacts in the MRI data can be prevented by a sensible experimental setup. To preserve the magnetic fields’ homogeneity within the scanner room, the utilized EEG system has to be made from exclusively para- or diamagnetic materials. Generally, appropriately shielding electrode leads and other materials as well as choosing MRI-compatible equipment is essential to the data quality, but even more important to the subject’s safety (Lemieux, Allen, Franconi, Symms, & Fish, 1997). Attaching electrodes to a subject in the scanner environment creates risks, such as electrodes heating up and causing severe burn injuries, depending on the EPI sequence and the strength of the magnetic field (Yeung, Susil, & Atalar, 2002).

In spite of these artefacts and safety requirements, simultaneous compared to separate EEG-fMRI recordings yield the greater potential. While free from artefacts, separate recordings do not represent identical psychological processes in test subjects. No brain activation at a given time point in a given experiment can be perfectly replicated. Using human subjects implies that the dependent variable (i.e., physiological signal variation) is influenced by several individual processes, which experimenters are unable to account for. Even when performing identical experiments with the same experimental protocol, the timelines of signal changes in the two experiments eventually diverge. Thus, in separate EEG-fMRI it is ill-advised to relate for instance single-trial EEG and fMRI signals, because they were acquired successively instead of concurrently. Other problems, such as training effects, habituation or fatigue, further add to the limitations of separate recordings.

Perhaps even more notable than the complementing spatial and temporal resolutions in combined EEG and fMRI is the benefit stemming from their physiological relation. Variation in LFP often bears more similarity to changes in BOLD than to recordings of single cell activity or MUA (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). At the same time, it is irrefutable that EEG and fMRI represent brain activity from two very different perspectives. Considering their physiological basis, it seems plausible that modulations across experimental conditions of BOLD and EEG activity do not align all the time (Im, Jung, & Fujimaki, 2005; Nunez & Silberstein, 2000). Whereas EEG signals only show the result of multiple, non-linear activity summations across cortical layers, changes in the BOLD signal reflect variations of oxygen concentration in different brain regions over time.

The fact that the two signals do not vary identically can be regarded as an upside and a downside to concurrent EEG and fMRI recordings. For one, non-coinciding variation of neuronal activity and cerebral blood flow, also referred to as neurovascular decoupling, could be seen as impeding to the validation of a result. If the multimodal results do not correspond, this might shed doubt on a significant finding, which is discovered in one method but not the other, although the one significant finding might still be meaningful. However, when relating, for instance, event-related potentials (ERP) to functional contrasts, neurovascular coupling would yield both results to be more meaningful. Plus, information from both sides aid the interpretation and integration of results into the greater theoretical background. Here, neurovascular decoupling might provide information as relevant as neurovascular coupling (Rosa, Daunizeau, & Friston, 2010). Decoupling could be merely the result of failed signal detection or it could be entirely unrelated to experimental conditions. However, it could also be attributed to pathological characteristics (Schridde et al., 2008).

Lastly, finding discrete variances in EEG and fMRI data can be regarded as a great advantage to single recordings, since it supports statistical predictions. Capitalizing on a larger variety of physiological signals aids predictive modeling by, for instance, either constraining or enriching a single signal’s prediction with the other (Turner et al., 2013; Turner et al., 2016; Turner, Sederberg, Brown, & Steyvers, 2013). Multiple investigations from Turner et al. (e.g., Turner, Forstmann, et al., 2013; Turner et al., 2016; Turner, Sederberg, et al., 2013) revealed a significant advantage of multimodal predictors as compared to single EEG or MRI regressors. Hence, integrating the two signals holds the potential to achieve a better understanding of how brain activity relates to behavior. This advantage is not to be underestimated, since the weak correlations of functional or electrophysiological findings to a subject’s behavior have often been puzzling as to how otherwise promising experimental results can be interpreted. Paying tribute to the fact that the measures used in these predictions only make up a limited part of brain activity, a joint approach opens up the possibility of testing the predictive value of multiple regressors.

Event-related

Unrelated

**EEG**

**fMRI**

Fig. 1. Illustration of variance proportions in EEG and fMRI signal attributed uniquely to EEG (red) or fMRI (blue) and event-related neurovascular coupling (striped) or event-unrelated coupling (not striped shared area) adapted from Herrmann and Debener (2007).

As a result, approaches for combined EEG-fMRI recordings allow analyzing shared and discrete signal variation (see Fig. 1) in the respective data sets (Herrmann & Debener, 2008). Highlighting neurovascular coupling and decoupling promises new insights for the study of physiological foundations of EEG and fMRI as wells as opportunities for testing hypotheses in the experimental investigations of cognitive processes.

For example, in decision making research combined EEG-fMRI has already been applied in a framework for outlining how spatio-temporal measures derived from both methods can change as a function of rising task complexity and how they can predict performance in a delay discounting task (DDT; Kyathanahally, Franco-Watkins, Zhang, Calhoun, & Deshpande, 2016). The latter requires the exertion of cognitive control, which can be considered the ability to adaptively recruit cognitive resources and subordinate executive functions in a manner that is beneficial and compatible to a person’s goals. In delaying an expected reward, the gain can be maximized, which might be momentarily dissatisfying, but more remunerating in the long-term. In order to suspend the need for reward, prepotent reactions need to inhibited, while keeping in mind context information about how behavior and rewards can be optimized. In their theoretical framework Dual Mechanisms of Cognitive Control (DMC) Braver, Gray and Burgess (2007) postulated two distinct modes, in which cognitive control operates, to explain inter- as well as intraindividual variability of working memory (WM) performance: 1) proactive control (i.e., anticipatory planning, early information selection, context-driven) and 2) reactive control (i.e., flexible behavioral adaptation, late correction, stimulus-driven).

There is substantial evidence that proactive control, as the mode that optimizes behavior, is the more resource demanding and puts a larger load on WM (Braver, 2012; Braver, Cole, & Yarkoni, 2010; Braver, Reynolds, & Donaldson, 2003). However, conceptually, proactive control is intended to rely on context information with a high predictive value and goal relevance. Therefore, decisions can be made at an early point and outcomes are maximized (Braver, 2012). Further, as classic theories of motor control already hypothesized (e.g., Feldman, 1986), optimal behavior in relation to cognitive resources is achieved through automatization and reduction of conscious effort. According to a theory of optimal motor control (Emanuel Todorov & Jordan, 2002; Emmanuel Todorov & Jordan, 1889) and equilibrium point control (Bizzi, Hogan, Mussa-Ivaldi, & Giszter, 1992; Feldman, 1986), adding prefrontal control to a routine task execution in a highly predictable environment is detrimental to the performance, since the involvement of the prefrontal cortex disrupts automatic control loops which would act faster on their own account. Still, considering proactive behavior that actually requires remembering a complex plan or information sequence necessary for task performance, it becomes apparent that proactive control cannot be a unitary construct. Instead, it probably constitutes an underlying pattern of how predictions form our behavior in the long-term, but can be executed in a resource demanding or automatized fashion.

Investigating this hypothesis is a challenging research undertaking, since a wealth of information is needed. To test the involvement of prefrontal structures associated with cognitive control, such as the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC; Barch et al., 2010; Botvinick & Braver, 2015; MacDonald, Cohen, Stenger, & Carter, 2000), spatial data is needed. Furthermore, the exact time course and identification of goal-relevant information is best highlighted in ERPs and ERSPs. To test if a subject forms a decision at an early point of task performance, visual potentials of information selection as the N1 or P2 (Chen et al., 2014; Kirmizi-Alsan et al., 2006) as well as later positive potentials connected to WM updating (Barcel & Cooper, 2017; Mento, Tarantino, Vallesi, & Bisiacchi, 2015; Polich & Criado, 2006) in response to context information should be analyzed. Proactive control, which is exerted by first taking in information into WM and then maintaining it via a dopaminergic gating mechanism (Braver et al., 2007), can likely be studied through observing these correlates of maintenance and updating information processing in WM (Polich, 2007; Polich & Criado, 2006). In addition to these ERPs, event-related spectral perturbation (ERSP) in the alpha (i.e., 8-12 Hz) as well as theta (i.e., 4-7 Hz) spectrum lend insight into synchronization of cognitive resources to support behavioral planning and correction (Griesmayr et al., 2014; Hwang, Ghuman, Manoach, Jones, & Luna, 2016; Murias, Swanson, & Srinivasan, 2007). Their exact function can further be assessed by, for instance, adding spatial data associated with the onset of oscillatory alpha synchronization (Gonçalves et al., 2005; Jann et al., 2009).

Thus, clarifying how cognitive control, in particular proactive control, governs behavior represents a promising research opportunity for joining EEG and fMRI data. It is perfectly suited to provide more precise neuronal correlates of cognitive processing, as has been done in the case of reactive control in unpredictable environments. By relating early ERPs associated with visual attention (i.e., N170) and increased alpha band power over the medial prefrontal cortex with increased BOLD responses in the supplementary motor cortex (SMC), Albares et al. (2014) have provided evidence for the neural circuitry coupled with precise temporal dynamics underlying flexible behavioral correction to unforeseen changes of environmental demands for goal-achievement. Consequently, enriched neuronal correlates enable a more sophisticated discussion and interpretation of experimental results.

Generally in biological psychiatry and psychology, neuroscientific methods like EEG and fMRI are applied to study mental processing. For a psychological phenomenon, which is not yet fully understood, researchers struggle to identify physiological correlates, which they do not fully understand either. This basic dilemma can also be found in clinical studies of biomarkers. In order to separate groups of patients and healthy controls or to improve the accuracy of prognoses for patients, clinical researchers strive to detect reliable biomarkers of a specific pathology (Fu & Costafreda, 2013; McGorry et al., 2014). Still, in clinical research these biomarkers, be it in EEG, sMRI, fMRI or in-vitro studies, of either pathological symptoms or higher cognitive functions tend to be unprecise (Venkatasubramanian & Keshavan, 2016). This can be attributed to small sample sizes, symptom overlap in patient groups, a focus on purely symptom-correlated markers, poor methodology, fundamentally insufficient understanding of the involved cognitive processes or any number of additional flaws (Sprooten et al., 2017).

A reliable way to combat these issues is to refine methodologies by either perfecting existing procedures, such as pre-processing or higher statistical analyses, taking advantage of emerging approaches for handling vast amounts of data (i.e., machine learning) or by enriching study designs with multiple methods (Fu & Costafreda, 2013). Through these innovations the consistency of clinical and non-clinical, neuronal correlates can be assessed and evaluated. Hence, combining methods is not only a promising scientific paradigm shift for basic research, but also for clinical applications. Better characterizing the sensitivity and discriminatory power for specific pathologies or their development might allow for more precise prognoses (Nouretdinov et al., 2010), predicting treatment responsiveness (Ances et al., 2005; Robinson et al., 1999) or even more effective screening methods (Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005) in psychiatry.

## 1.2 Multivariate and asymmetric EEG and fMRI data integration

Despite the short time combined EEG and fMRI has been developing as a major research field, there is already a wealth of literature for statistical analyses (Laufs, 2012). Next to the isolated types of analyses, which can be performed with one modality alone (i.e., ERP, time-frequency analysis, fMRI contrasts, connectivity analysis), there is asymmetric types of data analysis, such as EEG-informed fMRI and fMRI-informed EEG. In both cases one of the two methods takes precedence over or excludes the other (Huster, Debener, & Eichele, 2012). Further, each of these analyses only uses part of the data.

As mentioned in section 1.1, EEG data suffers from poor spatial resolution and the so-called inverse as well as forward problem. Both label the same problem, but from different perspectives. A missing inverse solution denotes the lack of certainty about a neuronal source for a given electric potential in the EEG, whereas a forward solution would give insight into electric potentials created at the head surface from a given dipole in the brain. One problem with the former, for instance, is that both skull and brain shapes deviating from normalized head templates can distort the analysis (Ollikainen, Vauhkonen, Karjalainen, & Kaipio, 1999). Here, combined EEG-fMRI recordings present a useful tool for improving the creation of inverse and forward solutions. By informing the analysis procedure about anatomical idiosyncrasies of a subject via individual sMRI data, estimating the source of a potential becomes more reliable (Dale & Sereno, 1993).

Another way of enhancing the EEG analysis with MRI data is to perform connectivity analyses within the source space. As opposed to the sensor space, which represents the outer head model with EEG electrodes on top, the source space is a statistically created space where estimated neuronal sources for EEG potentials are located. In assuming there is a common space shared between EEG sources, dipole estimations require a template. Moreover, physiologically it is reasonable to assume that the successive or concurrent emergence of dipoles has interdependent effects on neuronal sources, as in MRI it is widely accepted that brain activity can be analyzed in its connectivity patterns between different brain regions. Brought to the EEG source space, the strength of connectivity (i.e., correlations between brain activities) can be assessed between EEG sources (Barzegaran & Knyazeva, 2017; Schoffelen & Gross, 2009). This, however, is predicated on a precise definition of brain areas as can be provided by sMRI data. Such connectivity analyses are often carried out using surface data (Nunez et al., 1997; Nunez & Srinivasan, 2006; Srinivasan, Winter, Ding, & Nunez, 2007). Yet, these models are difficult to interpret and often criticized for being unreliable. This is due to the lack of information on neuronal sources and due to the results being vulnerable to artefacts caused by conductance heterogeneity of brain layers.

Parallel to the enhancement of EEG analyses, entering MRI data into higher statistical models can also be improved by adding EEG data. One of the most widely spread and straightforward approaches in this research is to compute single-trial EEG parameters from continuous data. For instance, if there is significant ERSP in the theta band (i.e., 4-7 Hz), single-trial theta power can be extracted from the EEG data, convolved with an estimation of the hemodynamic response function (HRF) from the respective subject and fed as a parametrized EEG measure into the General Linear Model (GLM) of first level fMRI analysis (Debener, Ullsperger, Siegel, & Engel, 2006; Scheibe, Ullsperger, Sommer, & Heekeren, 2010). A basic schematic of the pre-processing and creation of the parametric regressors can be seen in Figure 2.

This approach has multiple advantages compared to the aforementioned MRI-informed EEG analyses. Firstly, it enables an estimation of the contribution of an EEG-derived parameter. Therefore, it allows insight into voxel activation presumably coupled to increased EEG activity, which could also be labelled as a measure for neurovascular coupling. Secondly and perhaps more notably, the estimation is not only performed on a single-subject level, but on a single-trial level. An important drawback to asymmetric data integration is that multimodal data is not fully synchronized. Instead, a small portion of one original data set is allowed to limit or inform the other data set. This, for example, accounts for source estimations in the EEG when only the sMRI data is utilized in the analysis. Considering the goal of a given integration attempt, this might be entirely sufficient. However, if the aim is to link EEG and MRI as much as possible, doing so on a single-trial level, as entering a parametric EEG-regressors into the MRI GLM allows, makes more sense. However, with explaining more variability in voxel activation patterns as the primary goal of this analysis, it can hardly be argued that it reveals any information about the EEG. Thus, it remains an EEG-informed fMRI analysis and an asymmetric way of thinking about multimodal results.



Fig. 2. Schematic procedure of pre-processing of EEG data (red arrows) as well as the computation of the EEG regressor for EEG-informed prediction of fMRI voxel activation (blue arrow), adapted from Debener et al. (2006).

In order to adequately test a hypothesis, such as joint increased theta, late positive potentials and decreased prefrontal BOLD responses being associated with proactive control, it seems implausible to have one data source taking precedence. Demonstrating that EEG-derived parametric regressors can add explanatory value in predicting significant voxel activation is merely ample evidence supporting the hypothesis. EEG regressors have to be averaged over an epoch to enter the GLM as a single value per trial, which is a misrepresentation of the original time course information. Moreover, the calculated results speak for additional variance explanation in functional contrasts. Therefore, a small fraction of the EEG data is related to a small fraction of the fMRI data. It is hard to argue that minimizing the utilized data is a valid representation of the supposedly underlying cognitive processes. The same would account for taking an MRI-informed source estimation and comparing it with EEG results; it would simply represent a fraction of data that has been integrated asymmetrically. More variance in both data sets can be tapped into when joining them. While still being meaningful, these results of asymmetric integration, for example, do not allow for the previously discussed improved validity or the inclusion of single trial variance from two multimodal data sets that is set as the integral goal in combining EEG and fMRI.

## 1.3 Approaches for multimodal data fusion

The main advantage of data fusion is that it represents a multivariate approach which attempts to take into account almost all available information (Huster et al., 2012; Sui, Adali, Yu, Chen, & Calhoun, 2012). As in supervised machine learning (Besserve et al., 2007; Pereira, Mitchell, & Botvinick, 2009), data fusion can be informed by categorical variables about the experiment (i.e., distinction between conditions) and can identify common signal sources in data sets associated with levels of the categorical variable (e.g., Haynes, 2009). Again, as in machine learning, the extent of informing data limiting the analysis can be varied. To multimodal data fusion as well there is blind, semi-blind or informed approaches (Sui et al., 2012). In addition to the specificity level of analyzed data and prior information of the analysis, common approaches can be distinguished by prerequisite statistical or physiological assumptions about one data modality, both or the relation between modalities.

### 1.3.1 Joint and Parallel Independent Component Analysis

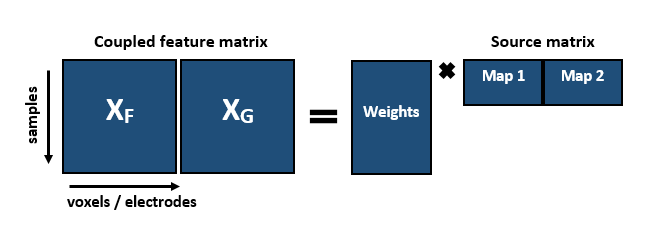
A popular method for fusing different kinds of medical imaging and EEG data is joint independent component analysis (jICA) (Calhoun, Adali, & Liu, 2006; Calhoun, Liu, & Adali, 2009; Eichele et al., 2008; Kyathanahally, Franco-Watkins, Zhang, Calhoun, & Deshpande, 2016). As with ICA in single modalities, a generative model with an unknown, linear mixing process of signal components is assumed to underlie the observed imaging or electrophysiological data. The basic idea of ICA is dimension or data reduction. At first, this might seem counter-intuitive, since the goal in data fusion is maximal data usage, but analyzing EEG and fMRI poses a severe problem to any type of signal decomposition, which is high dimensionality. With usual ICA in EEG, a two-dimensional data structure is explored (i.e., electrodes by time), which can be very conveniently displayed in an unmixing matrix. In a combined feature matrix with voxels from fMRI data, there is a large quantity of variables depicting a three-dimensional space being observed over time. This is a far more complex, multidimensional data structure, which, in order to be interpretable, has to be decomposed.

jICA aims at identifying maximally independent components from multiple sources contributing to the signal by unmixing signal parameters. However, a spatiotemporal decomposition, instead of a purely temporal or spatial one, is performed on at least two different data modalities to extract new features. In the context of multimodal data fusion, a feature refers to a data set, representing a relevant part of each data modality, which contributes to a data matrix as an input vector. In other words, it is a simpler data space to display links between modalities.

In terms of ERP and fMRI data, a spatio-temporal decomposition from jICA refers to the ERP time course and voxel intensity. However, the jICA adds a strong constraint by assuming that neuronal sources associated with the two data modalities vary the same way across subjects. Therefore, only features with identical linear covariation are extracted from the unmixed data matrix. Correspondingly, beta weights are assigned to pairs of components from both data modalities (see Fig. 3). When extracting complementary components from ERP time courses and fMRI contrasts, each time point in the extracted ERP time course is assigned a combination of the associated fMRI voxels, adding spatial to the temporal data. Here, of course, an assignment of voxel clusters to ERP time courses should not be interpreted as increased temporal resolution in the fMRI data, since the amount of observations (i.e., volumes) per variable (i.e., voxels) has not changed. Averaged voxel clusters associated with time points are better seen as a correlate of the variance found in the ERP time course.

The likelihood function used in the jICA is similar to common ICA as well. The joint unmixing data matrix W of two datasets and from the same sample of test subjects N is estimated so that the likelihood L(W) is maximal. In the estimated unmixing matrix each dataset has the dimensions N and voxels () or ERP time course (). The basic estimation of L(W) follows formula (1),

Fig. 3. Illustration of jICA with coupled feature matrix of multimodal datasets and in a shared data matrix (left) and in an umixed matrix with shared beta weights (right) adapted from Calhoun and Adali (2009).



,

where the vectors and represent observations for sample n = 1,… , N in the matrices and (Calhoun & Adali, 2009).

As mentioned in section 1.1, with this method for multimodal data fusion Kyathanahally et al. (2016) were able to detect decision making components underlying simple to more complex DDT. Joint components identified in simpler tasks with certain rewards could predict parts of activation patterns found in more complex tasks with reward and punishment uncertainty, indicating that decision making processes might occur in an additive fashion.

Although data fusion attempts to use all the available information, the jICA framework puts limitations to this principle. First of all, the constraint of identical modulation of features restricts the amount of data affecting the extraction of signal components. This constraint is necessary to focus on shared data sources. It can be relaxed by either choosing different datatypes or by switching to a semi-blind form of ICA-based signal separation. By assuming correlated instead of identical modulation of the datatypes, parallel ICA (pICA) performs a mostly identical signal decomposition as jICA. The most important difference lies in the relaxed, physiologically more accurate assumption about the relation of multimodal signals. On top of that, while the authors advise to use the jICA as a second level analysis on single subject data (e.g., Calhoun & Adali, 2009), other approaches have gone farther by performing data fusion on single trials (Debener et al., 2006; Huster et al., 2011; Murta, Hu, Tierney, Chaudhary, & Walker, 2016).

### 1.3.2 Multiway Partial Least Squares regression for EEG and fMRI

Multiway Partial Least Squares (N-PLS) (Bro, 1996; Mazziotta et al., 2004; McIntosh, Bookstein, Haxby, & Grady, 1996), like jICA, is a blind source separation method that lends itself ideally to explaining spatio-temporal, linear relationships between data sets. Unlike ICA-based approaches or similar dimension reduction methods, like principal component analysis (PCA), in N-PLS Singular Value Decomposition (SVD) is utilized (e.g., Harshman, 1970). SVD has been established as a handy tool for creating a decomposition of a matrix without forcing independence constraints to the components as in ICA. Therefore, there are less a priori restrictions on data decomposition.

When extracting features from multiple sets, N-PLS identifies those signal components from EEG data with maximal temporal covariance with certain BOLD profiles. Therein, the fMRI data is conceptualized as a matrix of voxels by time. From this matrix, the linear voxel combinations displaying maximal temporal covariance with components extracted from a second matrix (i.e., electrodes by time) are chosen. Next, a final covariance matrix of the relations between the original matrices of independent variable is build and decomposed with SVD (McIntosh et al., 1996). To account for the multi-dimensionality problem of combined data and for the abundance of variables in the fMRI, EEG data is reduced to a sum of so-called atoms each with specific spatial, temporal, and spectral factors. At the same time, fMRI voxel activations is decomposed to the same amount of atoms with a spatial and temporal dimension, so that each atom will have maximal covariance with its counterpart in the EEG (Mazziotta et al., 2004; McIntosh & Mišić, 2013).

Extracting data features from raw or single-trial data this way bears some pitfalls regardless of modality. For one, there is larger variability and noise levels to be expected. More than that, modeling data sets on such a precise level implies proneness to overfitting, since statistical models are adjusted until the empirical data can be estimated to the best extent (McIntosh & Mišić, 2013). As a result, N-PLS might fit noise in either data set to explain signal modulations. Finally, since no physiological assumptions before source separation are set, there is no guarantee that the resulting unmixing process represents the optimal or even a sensible model of the original neuronal processes in the subjects.

### 1.3.3 Multilevel Modeling

Lastly, since N-PLS and ICA serve the purposes of dimension reduction and relating different data sets, the last task remaining is connecting improved processing of neuronal data to behavioral measures. In the end, the criterion of predictive validity is often treated as a minor concern. While it is true that not all brain data can be related to a suitable correlate, since there a large gaps between the original brain activation and a behavioral equivalent, the pursuit of explaining behavior is still important. The idea behind understanding brain mechanisms is to make reliable predictions about people at some point, be it in a clinical or non-clinical context. Thus, even a negative test result from correlating an activation with a behavior can hold value.

One of the initial claims in section 1.1 and one that was put forward by Turner et al. (2016) is that enriching statistical predictors and methodology leads to enhanced prediction. If there is merit to the claim, EEG-, fMRI- or EEG-fMRI-based parameters should provide incremental contributions to explaining variance in reaction times (RT), error rates (ER) or other performance measures. However, it stands to reason if blindly entering variables into a predictive model serves any real purpose. Without any assumptions about the relation of predictor and criteria, significant explanatory value might be coincidental.

For testing the hypothesis of cumulative explanatory values in single and joint EEG-fMRI parameters, a multilevel model with an exploratory model sequence (Hox, 2010; Hox & Kreft, 1994) is perfectly suited for the task. The basic idea of multilevel models is that a hierarchical data structures causes dependent values to be more similar within naturally occurring subgroups. This applies, for instance, in a company where job satisfaction is more homogenous in specific departments or in task forces within the department. Transferring the example to an experimental setting, a subject’s performance levels might be more similar within measurement runs or within conditions of an experiment.

Parallel to the aforementioned examples, a multilevel model is a regressional model that allows for mixed linear effects performed on nested data. As such, data structures are organized in a manner that shows all observations collected from a subject ordered as repeated measurements within ascending categorical levels. As an example, an ERP measure would be entered as single-trial voltage values within a trialtype within a block or run within a subject. Consequently, a multilevel modeling approach ensures that there is less distortion of results due to false assumptions about homogenous or even unrelated distributions of dependent values or their residuals. In general, multilevel modeling benefits from being more robust (Maas & Hox, 2004), as they are less heavy on distributional assumptions than conventional inferential statistical models for comparing levels of multivariate designs (i.e., analysis of variance or covariance).

Furthermore, a multilevel approach lends itself to multimodal data fusion and prediction, since it allows for a sequential modeling of different types of effects. First, both slopes and intercepts of pre-defined experimental manipulations can be entered separately as random (i.e., residuals) or fixed effects. Second, these can be added as effects on different levels or as so-called cross-level-interactions, indicating the contribution of interactional effects between varying levels of multiple hierarchical predictors. Hence, the approach eases to assess the specific contributions of each step in an iterative specification of the most complex model (Hox, 2010). In an exploratory model sequence, this iteration can be tested by assessing the improved explanation of variance in the dependent variable with each added fixed or random model parameter. This is done by either observing changes in a model’s failure to account for variance (i.e., deviance) or by indexing a model’s fit on empirical data (i.e., goodness of fit criterion).

## 1.4 Aims of this study

### 1.4.1 Investigating mechanisms of cognitive control with EEG-fMRI

The main goal of this study is to present a framework of measures for both optimizing the processing and statistical modeling of combined EEG-fMRI data. Further, this framework shall be demonstrated on a specific example that benefits from having enriched data foundations and analysis. After all, next to the methodological concerns, the ideas collected in this framework were meant to serve researchers in neuroscience, psychology, medicine or other fields as tools for answering questions about mental processes.

Cognitive control, as the ability to flexibly regulate and control cognitive resources in a goal-oriented manner, has great value to clinical research. Populations suffering from deficits in this ability range from eating disorders (Tchanturia et al., 2012; Volkow, Wang, & Baler, 2011) and schizophrenia (Berger et al., 2016; Lesh, Niendam, Minzenberg, & Carter, 2011; Poppe et al., 2016) to drug addiction (Tang, Posner, Rothbart, & Volkow, 2015; Wiers, Gladwin, Hofmann, Salemink, & Ridderinkhof, 2013). Particularly the latter display reduced proactive control capacity to perform adequate behavioral perseverance or adaptation to long-term goals when stimuli, which are relevant for the addiction, are present (e.g. Brevers et al., 2017). Therefore, understanding cognitive control mechanisms might lead to a more refined knowledge of the associated disorders. As stated at the end of section 1.1, precise neuronal correlates can aid clinical predictions concerning treatment responsiveness or the development of the disorder.

In adapting a continuous performance task (CPT), originally designed for measuring cognitive control functions in schizophrenic patients (Henderson et al., 2012), for simultaneous recordings, this study aims at comparing the outlined approaches. The neuronal correlates of cognitive control in WM, as assessed in the Dot Pattern Expectancy (DPX) task or AX Continuous Performance task (AX-CPT), in both EEG and fMRI have already been studied extensively (e.g. D’Ardenne et al., 2012; Lopez-Garcia, Lesh, Salo, & Barch, 2016; MacDonald et al., 2005). For this reason, the DPX task adequately matches the purposes of this study. The existing literature on the task and proves its compatibility with both EEG and fMRI.

Past research points to the DLPFC to be the core structure of the two main control strategies in WM. In this task, long-term goal maintenance optimizes behavior. Subjects learn how to process predictive information imperative to their task performance. If they are successful, they should learn to identify the reliable context, reduce cognitive effort and simply maintain the goal-relevant behavioral strategy. Therefore, proactive cue maintenance should be less demanding than information updating and behavioral correction in terms of prefrontal cortex resources as compared to ambiguous context cues. In turn, it should involve larger parts of central and posterior parietal cortex (i.e., motor preparation). Concerning late behavioral correction, as applied in situations with uncertain contingencies, the anterior cingulate cortex (ACC) should be activated. Similar differences in neural activity should be found in ERPs. In particular, late frontoparietal positivity associated with WM updating and maintenance (i.e., P3, late sustained positivity) should relate to the processing of predictive context cues, due to the evaluation of an essential information for goal-pursuit at a later stage of cognitive decision making.

To our knowledge there have been no attempts at investigating these correlates in simultaneous EEG and fMRI recordings. Therefore, another secondary goal of this study is to replicate results from past, isolated EEG and fMRI studies on cognitive control in the DPX task.

### 1.4.2 The practicability of multimodal data fusion

Finally, since the primary goal of this study is to evaluate the practicability of multimodal data fusion, results unique or common to one or multiple analyses compared to unimodal data analyses (i.e., isolated EEG or fMRI) special focus shall be put on their discussion.

Taken together, jICA and pICA, N-PLS and multilevel modeling of EEG-fMRI data represent different approaches to data fusion. Each covers different aspects of neurovascular coupling and decoupling. They vary in how much information they utilize, which specific measures of fMRI or EEG are entered and in the physiological or statistical assumptions they make. Hence, they form a promising collection of analyses for evaluating benefits and drawbacks of multimodal data fusion.

By highlighting differences and similarities between approaches, the framework put forth shall be an indication as to how specific research questions can be more accurately addresses by corresponding analyses. This methodological focus promises to improve the glaring flaw of poor validity and interpretational issues in neuroscientific research. As such, each approach shall be discussed in regards to its contribution in explaining results on cognitive control mechanisms involved in the utilized DPX task.

# 2. Methods

## 2.1 Participants

For the experiment Thirteen healthy, right-handed medicine students from the University of Marburg (7 males and 6 females) were recruited. Each of them took part in an MRI introduction course to familiarize themselves method and to experience having an MRI scan performed on themselves. Subjects were additionally offered to participate in an fMRI experiment. If they agreed, subjects were asked permission to have an EEG recording added to the experiment. In exchange, they were provided an anatomical scan of their brain. Subjects were excluded from the experiment if they were not between 18 and 35 years old, reported impaired vision, left-handedness, prior experience with the task, current use of prescription drugs and acute or a history of neurological or psychiatric disorders. All subjects were between 18 and 32 years old (M = 23.23, SD = 4.28). Participants provided informed consent after they were given a summary of the risks and requirements involved as well as a rough outlet of the experimental procedure. This study was approved by the local ethics committee at the Department of Psychology.

## 2.2 Experimental Design and Setup

### 2.2.1 General Procedure

### 

All experiments were performed on the premises of the section for brainimaging located at the clinic for psychiatry and psychotherapy at the Department of Medicine in Marburg. When subjects arrived at the clinic, they were greeted and asked to take a seat in front of a desk in a comfortable office chair in a light-attenuated room. The desk was empty, except for a few sheets of paper, a stop watch and a pen. Starting from this point, all experimental procedures were documented on the standardized protocol (see Appendix 1).

Next, subjects were provided an oral overview of the following proceedings (i.e., conditions for participation, informed consent, etc.) and the study’s background. Then, they were handed the written version of the informed consent as well as a metal anamnesis to assess risk factors for the application of fMRI and to ensure the subject’s safety (see Appendix 2 and 3). The latter was used to ensure that there were no pieces of metal or electrical devices permanently attached to the subject’s body. On request subjects could receive a written report, describing the study’s background, risks and conditions of participation in detail.

If the subject had filled out all forms and had no further questions, the interviewer conducted pre-experimental interview (see Appendix 4), in order to assess demographic and personal data (i.e., age, highest academic degree, average grades). Further, to control for the influence of stable capacities for informational load, the Digit Symbol Coding Test from the German version of the Wechsler Intelligence Scale for Adults (WAIS-IV, fourth eidition; Petermann, 2012) was administered as a pretest (see Appendix 5). This measure was also included to enrich the battery of behavioral and self-report variables, which should be predictable by brain activation, with a cognitive test.

Afterwards, subjects were brought into the MRI control room, where they could change into a hospital gown. This was offered to prevent soiling the participants’ private clothing with gel from the EEG and ECG electrodes at the head and upper back. While subjects sat in a chair in front of the computer running the EEG and ECG recording software, the experimenter could check the signal quality (i.e., electrical impedance, voltage at each electrode). Two sizes of EEG caps were available (size 56-58 cm and 58-60 cm) with mounts for 31 ring electrodes plus one grounding (AFz) and one reference channel (FCz) on the fronto-anterior and fronto-central scalp positions, respecitvely.

Before the EEG cap was put on, skin portions that would be covered were cleaned with Isopropanol (70%), followed by measuring the subject’s head circumference. By assessing the distances between the left and right preauricular points as well as between the nasion below the forehead and the inion at the back of the head, the central vertex point (Cz) was marked as the intersection of the two axes (Klem, Lüders, Jasper, & Elger, 1999). The EEG cap was then put on at this central position. An elastic chin band prevented the cap from sliding.

Electrical impedances were reduced with a conductive electrolyte gel, containing pumice, as this gel component aids roughening the skin and removes detrimental elements to the electrical conductance such as callus skin or fat. The gel was distributed across the electrode sites, starting with the reference and grounding electrodes. For this purpose blunt plastic syringes were used, after slightly roughening the skin with cotton swabs. These were also applied for pushing away hair blocking the contact of the electrodes to the scalp. All impedances were kept at or below 5 kΩ. At last, the ECG electrode integrated in the EEG system was placed on the upper back. Before the electrode was attached and the impedance was optimized, subjects were asked if they preferred a person of the same sex to execute this step.

When the EEG and ECG signal were optimal, subjects were lead into the scanning room to the MRI bore. Here, several measures, as can be read in protocols from Ritter and Villringer (2006) or Mullinger, Castellone, & Bowtell (2013), were met to achieve optimal data quality. For a detailed description on these measures specific for simultaneous recordings, see section 2.3.2. During the entire time in the scanner, subjects were able to communicate with the experimenter via a two-way intercom system connecting the two adjacent rooms.

Following an anatomical T1-weighted scan, subjects were introduced to the DPX (see section 2.2.2) on ten slides with written instructions. When they felt confident, they could start with 18 practice trials. As opposed to the subsequent four experimental blocks, subjects received feedback on their performance (‘correct’, ‘incorrect’, ‘too slow’, ‘too early, please wait for the probe’). The feedback was initially given to make sure subjects had properly understood the task. Before the experiment and the functional data acquisition was started, subjects were asked one last time if they were well and ready to begin. From that point on, not counting practice trials and instructions, the experiment lasted approximately 32 minutes.

Finally, when the task was over, subjects were moved out of the scanner, freed of all EEG equipment and provided the opportunity to wash their hair and back. When they had cleaned themselves, all subjects participated in a post-experimental interview (see Appendix 6). Among other questions, they were asked how they rated their task performance on a scale of one to ten and which ideas they had on the purpose of the task. Concluding the experiment, subjects were informed about the background of the task and the complete purposes of the study (i.e., psychological mechanisms involved in DPX, clinical applications). In case they were interested, subjects could indicate if they wanted to be notified of the results of the study.

### 2.2.2 DPX Paradigm

The DPX task is a continuous performance task with four different trialtypes (AX, BX, AY, BY) repeated across experimental blocks. Each block consisted of 52 trials with four different trialtypes (AX, BX, AY, BY). Blocks were separated by one minute breaks and preceded by 18 practice trials. One trial consisted of two stimulus types. Stimuli consisted of dot patterns highlighted within a square of nine equidistant, blue dots. The first dot pattern (i.e., the cue) was presented in light blue for 100 ms on a white background, followed by a jittered interstimulus interval of 3 to 5 seconds. The second dot pattern (i.e., the probe) was presented in grey. As soon as the probe appeared, subjects had a time window of 800 ms to respond. After 300 ms the probe disappeared. A jittered intertrialinterval of 2.5 to 4.5 seconds separated the probe from the next cue. Thus, the minimum duration of each trial was 6.4 s and the maximum duration 10.4 s.

Subjects were instructed to respond with a right button push after a correct cue-probe combination and with a left button push after an incorrect combination. In the correct combination (AX) there was a vertical line of three blue dots on top of one another as a cue. The corresponding probe had the two upper dots of the vertical line and one on the right in the middle in white. Any deviation in the cue, probe or in both was considered incorrect. All patterns were constructed starting with of nine equidistant dots arranged in a square.

ISI 2.5 to 4.5 s

maintenance interval

**Right button**

Correct cue-probe combination **AX**

**BX**

**AY**

**BY**

Fig. 4. Illustration of the DPX task adapted for simultaneous EEG-fMRI recordings. One trial consists of a cue lighting up within in the square, followed by a mask and then the probe appearing in grey (left side of the figure). A correct combination is presented on the left and all incorrect combinations on the right side.

Incorrect cue-probe combinations

**Left button**

Across the four blocks 208 trials were presented with 136 AX (65%) and 24 trials (11.6%) for BX, AY and BY respectively. However, due to an error in the programming the fourth block consisted of 33 AX and 7 BX trials. Therefore, the actual amount is 135 AX, 25 BX and 24 AY and BY trials. An overview of the paradigm is given in Figure 3.

As often found in EEG paradigms, this design was intentionally unbalanced. For the paradigm to work, the correct trialtype AX had to have the highest frequency of occurance. Of the 52 trials per block, 33 were AX (65%) and 8 trials were each of the remaining trialtypes (11.6%). Thus, subjects developed a dominant response tendency towards AX to push the right button. However, in a small amount of trials (i.e., AY trials) the expectation to see a correct probe after a correct cue was violated. An AY trial required subjects to correct their behavioral planning by updating WM in a reactive control style. They had to integrate the unexpected information, since the last stimulus and not the context was imperative to their behavior.

By contrast, when subjects saw a wrong cue (B), a strong proactivity was triggered. Regardless of the probe, in a trial starting with a wrong cue there is only one possible response, since both cue and probe have to be correct in order for the trial to be correct. The wrong cue has to be maintained in WM, because in this case it is the imperative stimulus. As soon as subjects saw the correct probe, they had to inhibit the dominant response tendency to push the right button by having the context direct their behaviour. The last combination BY was a control condition and presumably did not require noteworthy cognitive control efforts.

Across the four blocks 564 trials were presented with 384 AX and 60 trials for BX, AY and BY respectively. Both the baseline and the dual demand blocks with cognitive reappraisal consisted of 282 trials. Hence, both conditions had 192 AX and 30 BX, AY and BY trials.

## 2.3 Data acquisition

### 2.3.1 Materials and software

### 2.3.2 Experimental protocol for simultaneous recordings

First, subjects were once more instructed about how to behave during the expriment. They were asked to abstain from any unnecessary movements of the head, torso or shoulders and to avoid crossing their limbs, as this would cause severe artefacts for both the EEG and fMRI. Furthermore, they were given a brief oral explanation of the experimental task. The participant’s head was then placed on a pressure-insensitive cushion and further stabilized with pads to minimize head movements. Electrode leads were passed through the head coil above the subject. Before moving the subject into the scanner bore, they were given an emergency control to be able to abort the experiment at any time they felt in danger. Inside the bore electrode leads were connected to the amplifier positioned behind the subject’s head. All cables and leads between electrodes and the amplifier were fastened with adhesive tape to either the head coil or the

### 2.3.3 Recording parameters for EEG and fMRI

## 2.4 Unimodal data analysis

### 2.4.1 Behavioral Data

### 2.4.2 fMRI pre-processing

### 2.4.3 EEG pre-processing

## 2.5 Multimodal data analysis

### 2.5.1 Asymmetric data integration

### 2.5.2 Joint and Parallel ICA

### 2.4.6 Multiway Partial Least Squares regression

### 2.4.7 Multilevel modeling

# 3. Results

# 4. Discussion

# 5. References

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