The role of glutamate in prediction error

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Abstract

The present study aims to investigate the molecular underpinning of the cognitive phenomenon *prediction error* by the use of functional proton magnetic resonance spectroscopy ($_1$H-fMRS). The phenomenon occurs when sensory stimulation deviates from predictions made by a cognitive model of the world. Theoretical considerations and empirical evidence from both basic and clinical research suggest that this phenomenon arises as a function of glutamatergic activity in the temporal and frontal cortices. $_1$H-fMRS has in recent years been used to successfully measure glutamate in response to sensory stimulation. The current study used an auditory oddball paradigm in order to investigate the possibility of measuring an increase in glutamate in response to auditory stimulation with $_1$H-fMRS, and investigate the hypothesis that glutamatergic activity underlies the prediction error phenomenon. The current study did not find any significant increases in response auditory stimulation in general but did find a statistically significant increase in response to auditory oddballs at 300ms and 400ms after stimulus onset. The current study also measured GABA in response to auditory stimulation. GABA was revealed to increase in response to auditory stimulation, showing a progressive increase from stimulus onset to 600ms. The current findings have implications for the use of $_1$H-fMRS to study metabolic activity in the brain, and for basic and clinical research pertaining to the functional role of glutamate and GABA in the auditory cortex.

Glutamate, GABA, $_1$H-fMRS, prediction error, Oddball

Sammendrag

Denne studien har som mål å undersøke det molekylære fundamentet til det kognitive fenomenet "prediction error" gjennom bruken av funksjonell proton magnetisk resonans spektroskopi ($_1$H-fMRS). Fenomenet oppstår når sensorisk stimulering avviker fra

prediksjoner generert av en kognitiv modell av verdenen. Teoretiske betraktninger og empirisk evidens fra både grunnforskning og klinisk forskning indikerer at dette fenomenet oppstår som en funksjon av glutamatenergisk aktivitet i temporal og frontale korteks. $_1$H-fMRS har de siste årene blitt brukt til å måle glutamat i respons til sensorisk stimulering. Denne studien benytter et auditivt "oddball" paradigme til å undersøke hypotesen om at glutamat aktivitet er fundamentet til "prediction error". Ingen generell økning i glutamat til auditiv stimulering ble avdekket av denne studien, men en signifikant økning i glutamat til avvikende stimulus 300ms og 400ms etter stimulering ble funnet. GABA ble også målt i respons til auditiv stimulering. En signifikant økning i GABA ble målt i respons auditiv stimulering, som progressivt økte fra 0ms til 600ms etter stimulus presentasjon. Funnene i studien har implikasjoner for bruken av $_1$H-fMRS til måling av metabolitt aktivitet, samt for grunnforskning og klinisk forskning rundt de funksjonelle rollene til glutamat og GABA i auditive korteks.

Preface

The project was presented as a master's topic during the last weeks of the spring semester 2019. The project really intrigued me, so I contacted the project leader Kristiina Kompus and we planned a meeting together. During the meeting I was briefed on the general aim of the study. We planned to meet again after the summer holiday and discuss the details of the project and my master thesis. After the summer holiday we had a meeting and worked out a plan for the study. Together we decided what direction to take the experiment, what experimental protocols to use and what metabolites to investigate. Gerard Eric Dwyer was brought in as a secondary supervisor and Alex Craven was consulted with regarding the technical possibilities and limitations of the study. After that I wrote up a project description and quickly started learning the necessary software to develop the experimental stimulus and protocols to be used in the study. Kjetil Vikene was also consulted with regarding frequency parameters for auditory stimulus. After the experimental protocol was developed, we ran pilot tests with EEG and sound recordings from the scanner in order to test if the auditory stimulus and the paradigm would work with the noise from the MR machine. After successful piloting I started developing the stimuli and the experimental protocols for the fMRS measurements and for the behavioral testing. The experimental parameters were calculated using a MATLAB algorithm developed by Alex Craven. I then recruited participants, ran the experiments, collected and analyzed the data.

First and foremost, I would like to thank Professor Kristiina Kompus for the opportunity to work on this project. Without her guidance, incredible knowledge and expertise this would not be possible. I would also like to give a special thanks to by co-supervisor Postdoctoral fellow Gerard Eric Dwyer, whose support, guidance and help made this master thesis possible. I would like to thank the staff engineer Alexander Richard Craig-Craven for all his help and expertise through this project. I would also like to thank Postdoctoral fellow

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Mismatch negativity

In the mid-sixties, Walter et al., (1964) conducted a series of experiments studying the event-related potentials (ERP) related to cognitive mechanisms preparing a subject for an upcoming "target" stimulus. These experiments used event-related designs in hope of studying endogenous cognitive mechanisms in the brain with the use of electroencephalography (EEG). The researchers discovered a cognitive ERP and coined it: *contigent negative variation* (CNV). With the increased signal to noise ratio allowed by the event-related design whereby specific time epochs could be timed locked with stimuli and averaged, this discovery was regarded as the first cognitive ERP, which subsequently heralded the field of cognitive science into a the modern day era of ERP research (Luck, 2014). Later experiments on attentional mechanisms of the auditory system and cognition revealed another important ERP (Hillyard et al., 1973; Näätänen et al., 1978). In a reinterpretation of previous findings and their own research revealing a negative deflection to rare *deviant* stimuli presented among more numerous *standard* stimuli, Näätänen et al. (1978) discovered and conceptualized the ERP "mismatch negativity" (MMN). They argued that auditory system automatically matches incoming stimuli to a memory "template" and that a mismatch between incoming stimuli and this memory trace or "template" is what resulted in this negative deflection occurring about 150ms after deviant stimulus onset. The researcher initially sought to investigate how attentional processes could detect relevant stimuli, looking for a relevance ERP, but Näätänen et al, (1978) deemed it a "deviation effect" to stimuli. The researchers suggested that the MMN likely indexed an auditory stimulus discrimination processes taking place in the auditory cortex and associated areas.

The MMN ERP was initial found in response to auditory stimulus. It has since its initial discovery been found in other sensory modalities and for more abstract features of stimuli pertaining to higher cognitive functions (Näätänen et al., 2007). The MMN and other electrophysical ERP's most likely arise from several generator processes, where a generator is a contribution of a neural population to the generation of these ERP's (Näätänen & Picton, 1987; Näätänen & Winkler, 1999). The MMN is calculated by segmenting the EEG measurements at the specific time epochs where the stimulus was presented (ERP's) and calculating the average for these. The average for the standard epochs is then subtracted from the average for the deviant epochs, resulting in a difference wave that reveal the MMN ERP (Näätänen et al., 2007). The MMN appears between 100-200ms over central and frontal regions of the scalp (Näätänen & Winkler, 1999). The phenomenon is normally probed using

an *oddball paradigm*. The paradigm involves presenting a train of frequent repetitive standard stimuli with less frequent deviating stimuli interspersed randomly in the train of standards (Duncan et al., 2009). This deviating stimulus can be any deviation in the stimulus characteristic from the standard, such as frequency, intensity and duration. The standard stimuli are all equal. Research involving magnetoencephalography (MEG) (Csépe et al., 1992; Hari et al., 1992), positron emission tomography (PET)(Müller et al., 2002; Tervaniemi et al., 2000) and functional magnetic resonance imaging (fMRI) (Jaaskelainen et al., 2004) have also measured this phenomenon (Näätänen et al., 2007).

The generators of the auditory MMN are found in the supratemporal region and the frontal region of the cortex, with the predominant part of the generators arising from the primary and secondary auditory cortices (Näätänen & Alho, 1995; Näätänen & Winkler, 1999). The origin of the temporal cortical generators has been confirmed using MEG, PET and fMRI (Näätänen et al., 2007). These generators have also been corroborated with direct evidence measuring the phenomenon with the use of intracortical recordings in the auditory cortex (Kropotov et al., 1995; Liasis et al., 2000; Rosburg et al., 2005). Kropotov and colleagues (1995) also argued that the mechanism underlying the MMN signal is separate from other functional systems, such as feature detection and attentional mechanisms, and works independently within the auditory cortex. The generators vary to some degree within the primary and secondary auditory cortex depending on the features of the stimulus being changed, revealing that different neural populations constitute different aspects of the signal, such as frequency, intensity and duration (Näätänen & Alho, 1995). There is also evidence for MMN generator enhancement for words, where the enhancement was found in areas normally associated with phonological and semantic processing of words (Näätänen et al., 2007). The frontal generator of the MMN signal may be involved in involuntary shift of attention (Alho, 1995; Rinne et al., 2000). This is indicated by an additional ERP: P300, which is used as an index for attentional shift (Näätänen, 1990). Lesions in temporal areas, specifically in the hippocampus have shown to diminished frontal P300, indicating a relationship between the memory function of the MMN and attentional shifts as indicated by the P300 (Knight, 1996).

The frontal MMN generators have been suggested to work in a reciprocal relationship with the temporal generators. Here, the initial MMN arises from generators in the temporal regions, which further activates frontal generators, that feed back into the MMN generator in the temporal region, which may help further guide the mechanism for detecting features which elicited the initial MMN (Näätänen & Alho, 1995). This interaction between temporal

and frontal mechanisms have also been studied using PET (Müller et al., 2002), where it was suggested based on the findings that the superior temporal gyrus (STG) is responsible for processing small changes and inferior frontal gyrus (IFG) for processing larger deviants. Research has suggested that the frontal regions are involved in monitoring expectancies and experience (Strange et al., 2000). Moreover, based on time difference in MMN generators, the temporal generators of the MMN signal are thought to drive frontal generators of MMN, leading to involuntary shift of attention (Rinne et al., 2000) Prefrontal areas have also been implicated in top down modulation of the auditory cortices, where they are suggested to tune the auditory change detection system by amplifying contrasts in smaller change between stimuli (Doeller et al., 2003; Opitz et al., 2002; Restuccia et al., 2005). More recent research indicate that the frontal and temporal areas show deviant detection to different timescales, where temporal generators respond more to local changes of stimuli, e.g changes from the immediate past, whereas frontal generators respond more to global changes, detecting changes in large timescales (Dürschmid et al., 2016)

Based on the research presented above, the generators of the MMN signal seem to be located in the temporal cortex and in the frontal cortex. The larger bulk of the signal seems to originate in the temporal regions, where there seems to be an interaction between the temporal and frontal areas. The signal seems to be driven by the temporal generators but modulated by frontal mechanisms. The theoretical consideration of the phenomenon will be considered in the next section.

Sensory Memory or Adaptation?

The sensory-memory hypothesis of the MMN index states that the MMN signal is a result of a mismatch between incoming sensory stimulus and a memory trace representing the sensory environment (Näätänen et al., 2005). This representation is argued to hold a model of the world by which the incoming stimulus is matched against. It depends on sensory memory to hold this representation, and a specialized mechanism tasked with monitoring the incoming stimuli is what results in the negative deflection. The MMN is proposed to represent a separate function from other ERPs and originate from unique generators separate from other ERP generators. Specifically, it is separate both neurally and functionally from an earlier "N1" ERP occurring at around 100ms after stimulus onset (Näätänen et al., 2007; Näätänen & Winkler, 1999). Proponents of the sensory-memory hypothesis argue that MMN constitutes a mechanism of sensory memory and might therefore reflect an inherently endogenous cognitive process (Näätänen et al., 2007). The N1, however, represents simple feature detector

processes, occurring due to exogenous activation by stimuli, arising from different generators than the MMN (Näätänen & Picton, 1987; Näätänen & Winkler, 1999).

This account of the MMN is contended by the adaptation hypothesis of the MMN phenomenon. The adaptation hypothesis postulates that the MMN ERP does not represent a mismatch detection function generated by a unique set of neurons, rather, it is a version of the earlier N1 ERP, which occurs due to fresh afferent neurons being activated by the deviant stimulus. It rests on known functions and properties of the neurons in the auditory cortex and other cortical areas (May & Tiitinen, 2010). The hypothesis asserts that adaptation of the standard stimulus relative to the deviant stimulus is the source of the difference wave measured when subtracting the standard epochs from the deviant epochs (May & Tiitinen, 2010). Adaptation is a form of habituation, which occurs when repeated presentations of identical stimuli result in an attenuation of activity in neurons specifically tuned to the those characteristics (Butler, 1968). The initial discovery of this habituation effect was done in a series of experiments where Butler (1968) found that by manipulating stimulus parameters the N1 signal could either be attenuated by keeping the stimulus characteristics constant and by decreasing the inter stimulus interval (ISI). But changing the parameters decreased the attenuation, and thus indicated that it lessened the habituation effect of repeating similar stimuli at short ISI. These findings were used by both proponents, where the sensory memory account took it as being the result of a mismatch detector, and proponents of the adaptation account (May & Tiitinen, 2010) took it as evidence for their fresh afferent account. The adaptation account subsequently used the habituation effect and later implemented lateral inhibition as a second function which would allow the hypothesis to adequately explain the MMN phenomenon (May et al., 1999). The adaptation hypothesis uses synaptic specific adaptation (SSA) and lateral inhibition in order to explain both the occurrence of the negative deflection but also the delay at which it occurs. Though adaptation and SSA can be defined differently, the former referring to an inherent function which is governed by neuron outputs and the latter referring to the specific adaptation to a stimulus (Malmierca et al., 2015), they are still used as analogs, meaning attenuation of activity due to stimulation. Lateral inhibition is the suppression of neural activity through inhibitory projections from adjacent neurons under stimulation (Houtgast, 1972).

Purporting the function of SSA in auditory cortex and its implication in generating the MMN signal, May and Tiitinen (2010) referred animal model studies showing that single neurons become attenuated as a result of SSA (Ulanovsky et al., 2003). The findings by

Ulanovsky et al (2003) also showed that stronger activation in N1 neurons to oddballs as a function of their lower probability of occurrence. Moreover, the latency of the deviant stimulus recordings changed as a function of the difference between standard and deviants, with smaller differences increasing the delay. The SSA was also diminished when ISI was increased. Although the delay of lessening the difference between the standard and deviant was only 16ms at most, the results are still viewed as supporting the adaptation account, by arguing the fresh afferents as being the main driving force behind the MMN signal (May & Tiitinen, 2010). The diminishment of SSA by increasing the ISI was also taken as an account for the temporal window of integration (TWI), which is a hallmark of the MMN signal. Although Ulanvosky et al. (2003) found a TWI of 1000ms, whereas the TWI for the MMN is found to be 200ms (Näätänen et al., 2007). Despite this, the parallel between the features of SSA and MMN are still viewed favorable by the adaptation hypothesis proponents (May & Tiitinen, 2010).

The adaptation hypothesis argues that the recurrent excitation and inhibitory regulation of activity in canonical microcircuits of excitatory and inhibitory (E/I circuits) neurons found in the cortex (Douglas & Martin, 2004) coupled with SSA and lateral inhibition is enough to account for the signal measured as MMN (May et al., 1999). Adaptation as a mechanism is a plausible explanation for why the standard signal becomes attenuated and lateral inhibition serves as a mechanism which explains the latency of the fresh afferents becoming active. Both adaptation and lateral inhibition are argued to be prominent features of the auditory cortex (May & Tiitinen, 2010). By suppressing neural population further away from the standard tuned cells, the signal is delayed when the inhibitory influence of lateral inhibition hyperpolarizes the neural populations tuned for the deviant stimulus which increases the amount of activation needed for reaching action potential thresholds (May et al., 1999). Lateral inhibition has been found to affect the neural firing outside the receptive field of that neuron to up to 50% in humans using invasive measuring (Howard et al., 1996) The N1 signal has also been found to be attenuated by both adaptation and lateral inhibition (Pantev et al., 2004). This conceptualization of how the N1 constitutes the MMN was studied using models which took into account the functional and physiological aspects of the auditory cortex. The predictions of the model was also tested empirically with EEG and MEG, which showed that adaptation and lateral inhibition were adequate for explaining the MMN phenomenon as a variant of N1 (May et al., 1999).

The notion that subtracting the standard ERP from the deviant ERP resulting in an ERP which itself serves as an index of a mismatch mechanism, or that this difference simply is a latency of earlier ERP, is a point of contention between the two hypotheses. Proponents of the adaptation account argue that arriving at the conclusion of an index of mismatching mechanism based on this method implies that the latency of N1 is invariant during stimulation (May & Tiitinen, 2010). This is pointed out by May and Tiitinen (2010) as flawed, arguing that even small changes in stimuli can "contaminate" the MMN signal, leading to an inflated MMN measurement where N1 constitute parts of this difference wave (Horváth et al., 2008). With increasing differences between standard stimuli and deviant stimuli, the more contamination the N1 signal has on the MMN signal, meaning that a larger portion of the MMN signal includes N1 generators (Schröger & Wolff, 1996). This can be controlled for by reducing the difference, but for MMN signals derived from "higher" cognitive deviation signals may be inherently flawed because the large difference in sound characteristics in for example vowels and words will cause this contamination regardless (May & Tiitinen, 2010). Control measures have been used to remedy potential contamination of N1 ERP's. By introducing a equiprobable tones including both the standard and deviants, and subtracting the deviant ERP's obtained from the oddball paradigm with the deviant tones obtained during the control measure, a more precise index of MMN can be calculated (Jacobsen et al., 2004; Jacobsen & Schröger, 2001). This has been proposed to help resolve the contamination problem of the N1 by sensory-memory proponents (Näätänen et al., 2007). The adaptation proponents argue that the parsimonious conclusion is to throw away the idea of MMN truly being an ERP constituted by its own neural population, and adapt a simpler explanation that the MMN simply is a delayed N1 signal due to difference in stimuli (May & Tiitinen, 2010).

When a train of standard stimuli is presented, any deviation within the TWI from this stimuli sequence will result in an MMN, even when the deviation from this sequence is an omission of sound (Yabe et al., 1998; Yabe et al., 1997). The omission MMN has been argued to speak in favor of professed endogenous process that the MMN represents and refuted the adaptation hypothesis by pointing to the fact that an omission of sound would not elicit any activation in "fresh afferents" (Näätänen et al., 2005). This phenomenon however is still argued to be explainable in adaptation account where it is argued that the ERP following omission deviants can be accounted for by rebound responses (RR) which is caused by a disturbance in excitatory and inhibitory (E/I) balance of the neural microcircuits found in the auditory cortex (May & Tiitinen, 2001). Although the neurons generating the N1 are thought

of as sensitive to specific characteristics, they are argued to form ensembles of circuits which contain neurons sensitive to temporal characteristics as well (He et al., 1997). May and Tiititen (2010) conceptualize that these neurons constitute spectro-temporal receptive fields (STRF), where neurons fire selectively to both the convolution of time- and physical characteristics of the sound itself into a unified receptive field. These STRF allow the auditory cortex to retain the temporal profile of stimuli, which is a crucial component of what constitutes sensory memory (Näätänen & Winkler, 1999). The response to omission deviants is explained by these fields, where simulation and empirical evidence have found that ISI of repeated stimuli is directly proportional to the latency of RR after stimulus omission (May & Tiitinen, 2001). The researchers explained the RR responses arise as a product of E/I circuitry, where these circuits essentially work as harmonic oscillators, synchronizing their activity to the stimulation rate through reiterative E/I activity. This gives the adaptation hypothesis an explanation for both how sensory memory might form physiologically and an account of the resulting latency to stimulus omission (May & Tiitinen, 2010).

According to Näätänen et al., (2007) the N1 and MMN ERP's represent different neural generators based on equivalent single dipole (ECD) calculation of MEG data (Csépe et al., 1992; Hari et al., 1992; Korzyukov et al., 1999; Rosburg et al., 2004; Sams et al., 1991). This is however refuted by proponents of the adaptation hypothesis, who claim that the technique does not warrant this conclusion, based on the fitting estimation of the ECD technique, fresh afferent activity from N1 neurons will bias the measurements in contrast to the neurons suppressed by the standard stimulus repetition (May & Tiitinen, 2010). Furthermore, the proponents point to recent evidence by (Jääskeläinen et al., 2004), who found multiple generators of the N1, some consisting of stimulus specific and some consisting of stimulus broad response patterns, which May and Tiitinen (2010) claimed to explain the ECD findings by placing the fitting parameters more in between specific and broad tuned neural population for the adapted neurons (standard specific), but more towards the highly activated neurons (deviant specific).

Although both hypotheses proclaim different accounts of what the MMN signal truly is, the point of contention seems to be the idea of N1 and MMN arise from different generators which implies that these constitute different neural ensembles (May & Tiitinen, 2010; Näätänen et al., 2007). These theories both postulate that the driving generators originate from supratemporal cortices and Heschl's gyrus, and both agree on the role of glutamate as being a driving force of the signal (May & Tiitinen, 2010; Näätänen et al., 2007).

Although these theories seem to conflict, both add valuable conceptualizations to the debate regarding the underlying physiology and cognitive constructs indexed as the MMN signal. The sensory-memory hypothesis conceptualize the MMN signal as indexing a cognitive construct, "sensory-memory" using a stimulus matching system to compare the model of the auditory environmental regularities to incoming stimuli (Näätänen et al., 2007). And the adaptation hypothesis conceptualizing and explaining the phenomenon in pure physiological terms, not particularly interested in explaining a physiological phenomenon in cognitive terms, but rather explaining the phenomenon in terms of otherwise simple functions such as adaptation, lateral inhibition and excitation/inhibition balances in the auditory cortex, and the subsequent computational properties (such as sensory memory) that may arise from these basic functions (May & Tiitinen, 2010). A third framework, which alleviates some of the dispute between the two latter hypotheses by unifying them based on the merits they bring to the debate is the predictive processing framework.

Predictive processing

The predictive processing (PP) account utilizes the phenomenon in an explanation of a larger framework seeking to explain all overarching tenets of human psychology. At the center of this framework is predictive processing, where the brain is seen as a prediction machine, constantly "guessing" or predicting the shape and structure of the next wave of sensory data, in many different temporal and spatial scales (Clark, 2015). In this framework predictions are conveyed via a hierarchy, by a top down model of the world, which attempt to match the incoming stimuli through backwards connection feeding predictions to a lower hierarchical layer. When this model doesn't fully predict the incoming stimulus, a prediction error signal propagates up through the hierarchical layers, which adjusts the parameters of the model to account for the prediction error (Clark, 2015; Friston, 2005). These signals are also regulated by context where canonical re-iterative E/I microcircuits combined with lateral connections are thought be assigned the role of regulating the "weighting" of the different prediction errors. This weighing is essentially a suppression of the prediction signals, helping contextualize the prediction errors and their subsequent impact on adjusting the model. These processes allows the brain to make inferences about the hidden states in the world (Friston et al., 2016). In this framework, the brain is structured hierarchical, in different computational layers, where each layer modulates the layer beneath, adjusting the predictions. This hierarchical conceptualization

fits well with the physiology of the brain, where the cortex can be seen as consisting of layers, each layers posing constraints on the layer below (Friston, 2005). The main driving force behind the predictive function of the brain in this framework is the minimizing of free energy. By reducing the prediction errors through adjustments to the model, the brain lowers the amount of energy expenditure needed to process information (Clark, 2015; Friston, 2005). The model that generates predictions is argued to be a generative model, using Bayesian principles of prior belief to infer the most likely causes of sensory data (Parr et al., 2018)

In order to explain the MMN, Friston (2005) asserts that the ERP to unexpected or rare event depends on learning the frequent stimuli, and therefore the hypothesis explaining the MMN in the PP network postulates that the ERP is a product of plastic connectivity changes mediated through perceptual learning and this signal is elicited when the system fails to suppress a prediction error, therefore the MMN can be regarded as indexing "prediction error". In order to test this hypothesis four models, built through dynamic causal modelling (DCM), were developed and compared using Bayesian model comparison procedure (Friston, 2005). These were developed based on two earlier neural models. An earlier model using evidence of how neural and cortical activity unfolds to emulate three classes of neurons and their function: Pyramidal cells (extrinsic excitatory), spiny stellate cells (intrinsic excitatory) and inhibitory cells (David & Friston, 2003). This model was combined with a minimal model developed by David et al., (2005), which was based on physiological data of the laminar organization of the cortex and the functional properties of these layers have via backward, forward and lateral connections. These parameters were made in line with laminar specific rules outlined by earlier research (Felleman & Van Essen, 1991; Friston, 2005). This allowed researchers to test individual modelling of forward(F), backward(B), forward and backward (FB) and forward, backward and lateral (FBL) neural systems up against simulation of neural systems. The model comparison found that the FBL adequately account for the MMN ERP as a function of perceptual learning (Friston, 2005). What emerges here is a system which both implicated E/I balances and plastic changes across a hierarchy of processing to account for the MMN signal. These findings didn't necessarily describe their model in pure PP terms, but simply showed what mechanisms could account for the MMN signal (Friston, 2005). However, newer simulation models have shown that the phenomenon can be adequately explained by these mechanisms in PP framework and at the same time illustrated the shortcomings of

the adaptation account which does not necessitate top down modulation (Wacongne et al., 2012). Neurocomputational modelling combining normative cognitive models and physiological models from fMRI have also been used to explain the MMN phenomenon and the effects of deviant probability and magnitude within PP terms (Lieder et al., 2013). However, the latter model proposed that predictive processing begins the thalamus, and not in the A1, but still conceptualizes the MMN signal recorded with EEG as an index of prediction error.

The comparison of the sensory-memory hypothesis, adaptation hypothesis and PP hypothesis in explaining prediction error have all been tested and compared (Garrido et al., 2008). The three theories were modelled in six networks, adapted from (Friston, 2005) and compared to EEG data collected during a roving oddball paradigm. Bayesian model comparison procedure revealed that the PP account of prediction error best accounted for the data (Garrido et al., 2008), by explaining the ERP as a failure to suppress prediction error signals via top down and lateral connections. Moreover, it has also been argued that not only did the PP proposition account for the data, but it can also accommodate for the same experimental findings that both the adaptation and sensory-memory can (Garrido et al., 2009).

Expectation and the subsequent suppression of expected events can be dichotomized by referring repetition suppression, which in an hierarchical sense, happens at a lower level where the conscious expectancy does not intervene with the system ability to suppress incoming stimuli, and expectation suppression which occurs at the conscious "higher" level where activity is suppressed by the conscious expectancy of an event occurring (Grotheer & Kovács, 2015). These two processes happen at apparently different time scales, which is argued by Grotheer and Kovács (2015) and illustrated by research by Wacongne et al., (2011), which found that lower level prediction errors are generated within a shorter time windows to more temporally local deviants, whereas higher level prediction errors are generated in response to deviation to global regularities in a larger time window. This can be indicative of a prediction error complex, where EEG indices such as the MMN consist of an early and a late component, where the later component is more sensitive to executive and attentional processes (Pegado et al., 2010). This seems to illustrate that as prediction errors move up the hierarchy, they become more apparent, consciously, to the agent. The dichotomy has also been argued to reflect a physiological component of prediction error in the temporal regions, and a more cognitive component of

prediction error in the frontal regions (Garrido et al., 2009). Where the signal reflects comparison mechanisms arising from the frontal regions and non-comparison mechanisms driving the signal in the temporal regions (Maess et al., 2007). More recently it has been argued that the lower cortical areas show a SSA mechanism, but as the signal propagates up the hierarchical system (from early sensory modalities to higher cortical areas in physiological terms) neurons in these higher areas seems to be showing an actual deviance detection mechanism (Sikkens et al., 2019).

The MMN index according to the PP account constitutes a prediction error which reflects both local changes of adaptation considered to be the precision weighing of predictions (adaptation account) and the plastic changes associated with learning between the different levels in the connective hierarchy (sensory memory) (Garrido et al., 2008). All the above-mentioned hypotheses implicate the role of glutamate in temporal lobe as the driving force of the prediction error signal and subsequently the MMN index as measured with EEG (Garrido et al., 2009; May & Tiitinen, 2010; Näätänen et al., 2007).

Glutamate

Glutamate is a ubiquitous amino acid which has a range of different functions both in the human body and the central nervous system (CNS). In the CNS it acts a as the main excitatory neurotransmitter and is a precursor to the main inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Erecińska & Silver, 1990). Pyramidal neurons have been found to account for nearly 70% of the neocortical population, where glutamate (according to animal models) has been found to constitute 35-70% of the excitatory activity of these neurons (Nieuwenhuys, 1994). Roughly 90% of synapses in the brain use small molecule amino acids as their neurotransmitters, where glutamate serves as the major neurotransmitter (Nicholls, 1993). Most cells in the nervous system contain at least one type of glutamate sensitive receptor (Zhou & Danbolt, 2014). The relationship between glutamate and GABA is tightly coupled in their interaction in neural circuitry of the cortex, where glutamatergic excitatory pyramidal neurons are regulated by inhibitory GABAergic interneurons. This allows these networks to go beyond an all-or-nothing activity structure that excitatory neurons alone offer, giving rise to complex computational properties like regulating excitatory feed-forward activity, spike generation and timing of output (Ferguson & Gao, 2018). These E/I networks form ensembles or microcircuits of neurons

mentioned earlier (Askew & Metherate, 2016; Logothetis, 2008). Sustaining a balance of glutamatergic activity is crucial for optimal cell functioning, where too high glutamate concentrations in the synaptic cleft can cause excitotoxicity, exciting the neuron to the point of destruction (Zhou & Danbolt, 2014).

The auditory cortex consists of many types of neurons and networks, among these are neural E/I ensembles (Blackwell & Geffen, 2017). When neurons in the A1 are stimulated, it elicits an excitatory postsynaptic potential (EPSP), which after a few milliseconds is followed by a longer lasting inhibitory post synaptic potential (IPSP) regulating this excitation (Askew & Metherate, 2016). The constant barrage of sounds from the outside world elicits a longer cascade of later EPSP's and IPSP's, which regulate cortical processing and ensure correct temporal timing and frequency tuning (Askew & Metherate, 2016; Blackwell & Geffen, 2017) This cascading excitatory and inhibitory effect of a stimulus onset can be roughly broken down into four sequential events consisting of glutamate and GABA receptors across pyramidal neurons and inhibitory interneurons: an early EPSP mediated by iontropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors is triggered, followed shortly by an IPSP mediated by GABA-A type receptors. As activity is regulated, a slower EPSP mediated by an ionotropic *N*-methyl-D-aspartate receptor (NMDA) receptor occur and subsequently a slower IPSP mediated by metabotropic GABA-B receptors respond to the later EPSP. The later EPSP mediated by the NMDA receptor is both suppressed and regulated by early and late IPSP's through hyperpolarizing. However, this inhibition can be relieved by suppressing the IPSP's (Askew & Metherate, 2016). Studies involving *in vitro* cell groups have supported the idea that these mechanisms serve as the neural underpinning of MMN index (prediction error). Here, ensembles of neurons initiate in slow NMDA mediated EPSP's modulated by IPSP's and can be measured as activity oscillation in the gamma range. The functional aspect of these later EPSP's and IPSP's *in vivo* are still not well understood. This also means that the characteristics of these mechanisms in relation to phenomena such as prediction error is still elusive. But due to the cell groups *in vitro* characteristics like time course, latency and sensitivity to glutamate antagonists, it lends credence to these mechanisms being a neurological foundation of prediction error (Askew & Metherate, 2016). Some studies aiming at investigating *In vivo* measures of this E/I balance using forward masking procedures, where the rapid presentation of two stimuli results in a suppression of activity for the second stimulus, attributed the hyperpolarization

(early IPSP) and suppression (late IPSP) effects to the regulation of excitatory NMDA activity. However, the later IPSP which lasts 200-300ms is argued as explaining only a small magnitude of this effect (Wehr & Zador, 2005). Although evidence is not clear cut, these consideration involve the NMDA receptor as taking a central role in the generation of the MMN signal (prediction error) (Askew & Metherate, 2016).

A more direct finding implicating glutamatergic NMDA receptors in the generation of prediction error came as a result of an animal study using pharmacological intervention to study the monkey equivalent of the MMN signal (Javitt et al., 1996). An oddball paradigm was used to elicit MMN signal. Researchers used a glutamate antagonist (Phencyclidine) that specifically targets NMDA receptors. Here results showed that MMN amplitude was significantly reduced after pharmacological intervention, which was indicative of the MMN signal reflecting NMDA activity within the primary auditory cortex. Similar results have been obtained in studies on humans using the glutamate antagonist ketamine, where a reduction in MMN was correlated with ketamine effects, but not N1 amplitudes (Umbricht et al., 2000; Umbricht et al., 2002). Umbricht et al. (2002) argued that due to the NMDA receptor's sensitivity to disinhibition of the membrane potential of neurons, it was particularly suited for mediating responses like the MMN. This finding has been replicated many times in both humans and in animal models (Ehrlichman et al., 2008; Kreitschmann-Andermahr, et al., 2001) and even when comparing the effects of ketamine to pharmaceutical which target other neurotransmitters (Heekeren et al., 2008; Schmidt et al., 2012; Daniel Umbricht et al., 2003).

An index of pathology

The MMN index has been found to be reduced in a range of different psychological pathologies (Näätänen et al., 2014). For instance, people suffering from dyslexia have shown reduction in MMN to pitch changes in auditory stimuli (Baldeweg et al., 1999), even when controlling for cognitive abilities and psychophysical measures (Stoodley et al., 2006). These reductions have been found to be remedied by audiovisual learning (Kujala et al., 2001), implicating plastic changes and learning mediated through NMDA receptors (Traynelis et al., 2010), which in turn implicate the role of NMDA in MMN signal generation (Askew & Metherate, 2016). This notion is also central in the "neural noise" hypothesis of dyslexia, which holds that hyperexcitability in glutamatergic system disrupts normal functioning of E/I circuits in the cortex, leading to suboptimal sensory input,

processing and neural timing maintenance (Hancock et al., 2017). Studies using MRS have found that higher concentration of glutamate are negatively correlated with reading and linguistic ability (Pugh et al., 2014). Although these measurements cannot say anything about the dynamic nature of E/I circuits, it still implicates high glutamate levels in dyslexia, which may cause the disruption in lower level systems which impact higher cognitive abilities and phonological representation for people with dyslexia (Hancock et al., 2017).

Lower amplitudes in MMN and hyperexcitability in glutamate have also been found in people suffering from bipolar disorder (Chitty et al., 2013). These researchers conducted two meta-analyses, reporting consistent results of higher glutamate levels in frontal regions and reduced amplitude of MMN in people suffering from bipolar disorder. Reduced amplitude in MMN have also been found in children with autism compared to non-autistic controls (Vlaskamp et al., 2017). Repetition suppression deficits have also been found to increase with the amount of autistic traits (Ewbank et al., 2015), which may indicate a failure of properly regulate inhibitory functions of E/I balances (Batista-Brito et al., 2018).

A pathology highly implicated in MMN research is Schizophrenia, where individuals suffering from this disease have consistently showed reduction in MMN amplitude (Umbricht & Krljes, 2005). The MMN has thus served as a potent index in clinical research of the disease (Garrido et al., 2009; Light & Näätänen, 2013). According to *The Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013), the disease is characterized by positive symptoms such as delusion, hallucinations, disorganized speech, grossly disorganized- or catatonic behavior and negative symptoms including affective flattening, alogia and diminished emotional expression. Impairments in cognition, memory, including working memory impairments and lower IQ is also associated with Schizophrenia (Baldeweg et al., 2004; Kremen et al., 2001; Rissling et al., 2013; Umbricht et al., 2000; Umbricht et al., 2002). Schizophrenia is also associated with reduced cortical volume in the frontal and temporal regions (Kong et al., 2012), and significant grey matter loss in the left temporal regions such as supratemporal cortex, planum temporal and transverse temporal gyrus (Heschl's gyrus) (Vita et al., 2012). The cortical loss in Heschl's gyrus has been found to be especially associated with the deficits found in the MMN amplitude for frequency deviants (Rasser et al., 2011). Although people with schizophrenia have shown reduction in a range of

different measurements and ERP's, MMN are among the most reduced (Light et al., 2012).

The cognitive deficits of schizophrenia have been shown to correlated with the MMN amplitude reduction, specifically a blunted memory trace of MMN (where decreasing probability of deviants increases MMN) was associated with cognitive impairment (Baldeweg et al., 2004). Here, Baldeweg et al (2004) argued that this could reflect a deficit in cortical adaptability. Moreover, the reduction in MMN has been suggested to reflect a loss of functional integration in the auditory cortex (Michie, 2001). The temporal and frontal regions have also shown loss in functional connectivity in people suffering from Schizophrenia (Winterer et al., 2003). Using healthy participants, the symptoms and cognitive deficits associated with Schizophrenia were temporarily induced via injecting an NMDA antagonist (Ketamine) (Umbricht et al., 2000; Umbricht et al., 2002). This implicates glutamate in the temporal and frontal regions as a potential candidate for understanding the neurobiology of the disease and subsequently the MMN index

Although neurotransmitter like serotonin(Eggers, 2013), dopamine (Meltzer & Stahl, 1976) and glutamate (Olney & Farber, 1995) have all been separately implicated as being the culprit in schizophrenia, contemporary theories implicate all these and their relations to one another (Stahl, 2018). However, NMDA receptors have been of special interest in implicating the prediction error index to Schizophrenia (Garrido et al., 2009)

The idea of prediction error and the diminished MMN signal are central themes and findings in support of the Dysconnection hypothesis of schizophrenia (Friston et al., 2016). The theory postulates that Schizophrenia and its symptoms (Delusions, Hallucinations, negative symptoms etc) are due to an anatomical and functional deficit in the brain. The theory explains schizophrenia in an PP framework. According to the theory, schizophrenia is caused by faulty NMDA receptors which lead to disruption in E/I balance of microcircuits which subsequently results in a failure to regulate the gain of activity (prediction errors), which is what normally allows for optimal inference (inferences about the state of the environment). The consequences of these imbalances give rise to symptoms such as hallucination and delusions. Delusions in this hypothesis are thought of as higher order hallucinations, which come from faulty inferences made by a broken prediction error weighing (Friston et al., 2016) The reduction in MMN found in those suffering from schizophrenia according to this framework comes from a faulty system which fails to properly modulate (contextualize) intrinsic and extrinsic connection in a hierarchical order

predictive brain (Friston et al., 2016) The role of the NMDA receptor in functional interactions between excitatory pyramidal neurons and inhibitory parvalbumin interneurons have been proposed as one of the possible aberrations present in Schizophrenia (Lewis & Moghaddam, 2006).

In the light of the predictive processing scheme, the difference wave that is measured as MMN and it's analogs can be illustrated as follows: When the system fails to properly suppress the prediction errors generated by the standard stimulus, the relative difference between the standard stimulus and the deviant stimulus decreases, which yields a reduced MMN amplitude. Biologically, this means that neurons are not properly suppressed during stimulation, most likely due to a faulty NMDA receptor functioning which fails to properly activate inhibitory GABAergic feedback neurons (Carlén et al., 2012), leading to a sustained activity in the pyramidal neurons stimulated by the standard stimulus. This also fits well with the neural noise hypothesis of Dyslexia, which involves aberrant glutamate activity in these microcircuits which leads suboptimal functioning (Hancock et al., 2017).

Nuclear magnetic resonance

The principle underlying both magnetic resonance imaging (MRI) and spectroscopy (MRS) is nuclear magnetic resonance (NMR), which is the process by which particles such as a hydrogen nucleus, may absorb and reemit electromagnetic radiation of a characteristic frequency (Lipton, 2008).

The physics that lay the foundation for the use of MRS and MRI is quite extensive, however, a brief summary of the processes that allow for capturing images and metabolic spectra of the brain is needed to appreciate the validity of this technology. In its simplest form, it gathers information from the resonance signals of atoms with nonzero spin, such as hydrogen atoms (Lipton, 2008). Hydrogen, found in water molecules, is the most abundant atom in the human body. The hydrogen atoms possess a quality known as *spin*. Spin refers to the property by which particles behave as if they are spinning around their own axis, possessing qualities which can allow classical physics to predict the angular momentum of these atoms if an external force (electromagnetic radiation) is applied (de Graaf, 2007). For an atom to have spin, it must have: protons and neutrons in odd numbers or either protons or neutrons in odd numbers. If an atom has even number of both protons and neutrons, it has zero spin. Due to the fact that hydrogen atoms only have one proton and no neutron, it

possesses spin, which makes the atom behave like a dipole aligning itself to an applied magnetic field (Lipton, 2008; Tognarelli et al., 2015)

When an external magnetic field is applied to the protons, they act as magnets, aligning either parallel or antiparallel to the applied magnetic field. The former is considered a low energy state and the latter a high energy state. It is the transition through these high and low energy states that the MRS capitalizes on. To make the protons transition between states, energy has to be applied. This is done by applying electromagnetic energy in the radio frequency (RF) range, set to the frequencies the protons resonate at. The frequencies at which protons resonate is proportional to the magnetic field, therefore their resonance can be calculated using the Larmor equation. Simply put, the Larmor equation states that magnetism is proportional to spin and therefore only nuclei possessing non-zero spin can undergo NMR (de Graaf, 2007). Normally spins are random and therefore their summed net magnetization is equal to zero. When exposed to the magnetic field, a small amount of the protons aligns with the applied magnetic field, which yields a net magnetization. This small excess magnetization in the parallel orientation is what allows for a signal to be detected. (Lipton, 2008). As the RF pulse is applied, the net magnetization will change orientation and "flip" to a 90° angle, perpendicular to the applied magnetic field. This is where the signal received by the sensors are the strongest (Barker et al., 2010). When the RF pulse is shut off, the protons will transition back to equilibrium. During this phase, their signal decays in two ways, spin-lattice (T1) relaxation, where the protons go from the high energy state to a lower energy state, and spin-spin relaxation (T2), where the spins diphase from each other causing a decay of the signal. Both these processes contribute to the signal decay known as free induction decay (FID). This is signal contains the all the resonance from the nuclei. This FID is decoded and presented as a spectrum of individual resonances through an arhythmical transformation known as the Fourier transform (Stagg & Rothman, 2013; Tognarelli et al., 2015). For studying processes in the brain, where water is quite abundant, proton MRS (^{1}H-MRS) which target nuclei (protons) of hydrogen atoms is often used. This method offers a rather large sensitivity relative to other nuclei (Barker & Lin, 2006).

Although hydrogen atoms exhibit the same resonance frequency, small differences in this signal are present due to the immediate molecular environment (chemical shift) and the binding of electrons of similar nuclei (J-coupling) which causes a shielding effect from the applied magnetic field. The differences that arise from these principles allow for the

separation and quantification of the different metabolites and the fluxes of their pathways according to their individual "spectroscopic fingerprints" (Stagg & Rothman, 2013). The resulting measurements of the frequency differences are in order of parts per million (ppm) and are usually measured and analyzed in reference to another reasonable stable and abundant metabolite (Stagg & Rothman, 2013). For most ^{1}H-MRS water is used as a reference. In the resulting spectrum metabolites are represented by a series of peaks, where the area beneath the peaks represents the quantities of the different metabolites, although their exact ratios are slightly off due to T1 and T2 relaxation effects (Tognarelli et al., 2015).

Recently, a new method of ^{1}H-MRS has emerged (Stanley & Raz, 2018). Using ^{1}H-MRS in a functional manner (^{1}H-fMRS), it may be used to track dynamic changes in neurochemistry much like its counterpart functional MRI (fMRI), which has been used to track hemodynamic changes in the brain (Logothetis, 2008; Mullins, 2018). ^{1}H-fMRS can thus be used with the same methodological designs as fMRI, such as event-related designs, to track changes in neurotransmitters in the brain within a temporal resolution of seconds (Mullins, 2018).

Traditionally spectroscopy has been used for capturing a temporally coarse spectrum of the resting metabolite composition of the brain. This new ^{1}H-fMRS, along with advancements in technology and techniques has shown the ability of capturing a more temporally refined and dynamic metabolite changes in response to experimental probing of cognitive mechanisms (Stanley & Raz, 2018). With the increasing magnetic field strengths (3, 4 and 7 Tesla) of MR machines the signal to noise ratio has subsequently increased, which allows researchers to benefit from the increased spectral, spatial and temporal resolution that comes with higher field strengths. Although fMRI has been extensively used for psychological research and inferences based on this research have been made between biological mechanisms and the cognitive constructs being measured, fMRI still utilizes a blood oxygen-level dependent (BOLD) measure which cannot properly distinguish between inhibitory and excitatory activity (Logothetis, 2008; Stanley & Raz, 2018). ^{1}H-fMRS gives researchers a perhaps more direct way of tracking neural activity through changes in neurotransmitter concentrations such as glutamate (Mullins, 2018). Event-related designs allow researchers to present rapid stimuli in a random order and segment these events into epochs, which are then analyzed and allow for tracking a response change over time (Tie et al., 2009). As Tie et al. (2009) point out, this is a well-

established technique in fMRI where later analysis allows for accurately measuring the hemodynamic response in response to the rapid stimuli being presented. For fMRS, a technique referred to as binning has provided as useful way of tracking glutamate change over time, where bins contain time locked acquisitions during experimental stimulation (Stanley et al., 2017).

The use of high magnetic field $_1$H-MRS was first shown to be able to measure changes in glutamate and glutamine in the anterior cingulate cortex in response to pain in 15 years ago (Mullins et al., 2005) and the techniques such as $_1$H-fMRS have since been developed to better track neurotransmitter changes in under experimental conditions (Mullins, 2018). The use of event-related designs for $_1$H-fMRS constitutes a smaller part of overall $_1$H-fMRS research, they do yield adequate increases in glutamate (Mullins, 2018). Although some of the initial studies showing great increases in glutamate using $_1$H-fMRS employed a paradigm in which pain was used to induce increases in glutamatergic activity (Cleve et al., 2015; Gussew et al., 2010; Gutzeit et al., 2011; Gutzeit et al., 2013; Mullins et al., 2005), more recent research has shown glutamate change as a function of cognitive mechanisms (Apšvalka et al., 2015; Bezalel et al., 2019; Jelen et al., 2019; Lally et al., 2014; Woodcock et al., 2018). The temporal resolution of MR is much coarser than that of EEG and MEG (Rao & Cecchi, 2012), which has been traditionally used for investigating prediction error under oddball paradigms (Fishman, 2014). This means that data processing is also slightly different, from an acquisition stance. Normally, the excellent temporal resolution of EEG allows for segmenting epochs belonging to time locked occurrences of the stimulus being used. By selecting the epoch when the stimulus appeared and averaging these together, an ERP signal emerges, as the averaging nullifies the random noise. With $_1$H-fMRS this can still be achieved by "binning" instances together, however this has to be done with stimulus which is presented at a rate which allows for synchronizing it with acquisition timing (Apšvalka et al., 2015)

For instance, Apšvalka et al. (2015) sought to investigate the glutamatergic activity associated with presentation of novel visual stimuli compared to repeated "standard" stimuli. Stimulus presentation lasted 700ms and was presented in blocks of 36 seconds. Water suppressed signals were acquired 250-300 ms after stimulus onset and water unsuppressed after 1700-1850ms after stimulus onset. The researchers were able to both analyze the data in a block design fashion, where the total Glx indices for the 36 second blocks are calculated, and event-related design, where each measurement for the two type

of stimuli are calculated and averaged. This was done to compare the two approaches to analysis and design. Here, both designs yielded a significant increase in glutamate during presentation of novel stimuli compared to repetitive stimuli. The researchers could also confirm that other measured metabolites remained stable, indicating that the increases in glutamate were not due to a generalize change in neural activity. This study among others give merits to the ability to track glutamatergic change with the use of event-related design in conjunction with $_1$H-fMRS (Lally et al., 2014).

The use of $_1$H-fMRS in an event-related fashion has not been used to investigate the prediction error phenomenon, but research using event-related $_1$H-fMRS has found increases in glutamate associated with increased gamma band oscillatory activity (Lally et al., 2014). Gamma-band activity has been associated with successful memory formation (Fell et al., 2001) and more recent research have found increase in gamma band activity in response to unexpected stimuli (Todorovic et al., 2011) Specifically, the researchers found an increase in gamma band activity when stimuli was highly expected, but omitted. These findings have been regarded as reflecting a failure of suppressing neural activity by top down prediction, indexing prediction error (Bastos et al., 2012). This has led researchers to speculate that prediction errors are communicated through superficial pyramidal cells in the gamma range (Friston et al., 2016). Moreover, Lally and colleagues (2014) sought to investigate how glutamate changed during gamma band activity induced by the presentation of either familiar or unfamiliar objects (object vs abstract image). The researchers speculated based on neural microcircuits consisting of E/I balances between GABA and Glutamate that this balance is essential for temporal tuning of activity. A change in glutamatergic activity was associated with stimulus related changes related in gamma band activity. Based on earlier research implicating AMPA, NMDA and GABA in eliciting gamma band oscillation, the researchers argue that the results added to the idea that GABA activity contribute to gamma frequency, but glutamatergic activity by itself is specifically associated with gamma-band oscillation power. Taken together, the use of $_1$H-fMRS to study associated changes in glutamate and gamma band activity, and considering that the gamma band activity have been linked with the propagation of prediction error signal, these results give some merit to the attempt of indexing larger changes in glutamate during deviance presentation relative to standard stimulus presentation.

Research questions

The glutamate level in the auditory cortex shows (1) increase to the presentation of any auditory stimulus across the post-stimulus onset time; (2) larger increase for the presentation of a stimulus that deviates from an established pattern compared to a 'standard' stimulus.

A change in GABA levels is also expected in response to deviant and standard stimuli.

Performance on auditory acuity tests and performance on behavioral auditory discrimination (1) to positively correlate; (2) the performance on auditory acuity test to explain the variance in behavioral auditory discrimination test.

Method

Participants

The demographic aimed to be recruited for this particular study was young participants in the range of 18 to 35 years of age. An estimated 10 to 15 participants were intended to be recruited. Sampling was based on self-selection, where participants were recruited using flyers around the campus area of the University of Bergen and Haukeland University hospital. Recruitment and experimentation took place between the beginning of February to mid-April. The recruitment posters contained information regarding the aim of the study, the inclusion criteria, total length of the participation and compensation for participating. A total of 15 participants were recruited for the study (age range: 20-27, M = 24.2, SD = 2.12), which consisted of 10 females and 5 males. Based on earlier studies, reliable indices of glutamate using $_1$H-fMRS had N = 10 (the calculated mode) (Mullins, 2018). Beyond the experiment for this master thesis, the study aims to collect N = 30. This was estimated with G*Power 3 (Heinrich-Heine-University, Dusseldorf) as an adequate sample size for detecting a statistically significant MRS signal in the brain to different manipulated variables with $\alpha = .05$ and a statistical power of .80.

Participants recruited for the study needed to meet the following criteria: Age between 18 and 35, right-handed, normal hearing and Norwegian/English comprehension, no history of psychiatric or neurological disorders nor currently taking medication for any of these, not pregnant, not having surgical implants with magnetic properties and no claustrophobia. Also, participants had to refrain from alcohol 24 hours prior to testing, and nicotine and caffeine 5 hours prior to testing. Right handedness was included due to findings indicating that left

handed people show atypical lateralization of function (Knecht et al., 2000) and atypical interhemispheric processing (Iwabuchi & Kirk, 2009).

Ethics

Study was applied to and was approved by Regional committees for medical and health research ethics (REK-case nr: 48827). All participants were compensated 200,- NOK for participation. All data collected and analyzed for this study is completely anonymized.

Procedure

Participants met two times for experimentation, either the same day or on the following day. First part of the experiment included signing written consent form and behavioral testing. Handedness, hearing and behavioral auditory discrimination was assessed in the auditory laboratory at the Institute for Biological and Medical Psychology. All participants had received a document outlining the aim and reason for the study beforehand via email but were given a copy before testing in case there was a wish to reread or any questions regarding the study. The second part of the experiment took part in the basement floor of Haukeland hospital. Participants were greeted by the radiographs upon arrival in MR room. Here, they were briefed on the experimental procedure and signed a document stating that they met the criteria for undergoing MR scanning. During experimentation, participants were given a call button in case they wished to contact the radiographs in the control room. During the 30 minutes of scanning, 20 minutes were dedicated to experimental protocol, where participants passively listened to the auditory experiment while watching the dvd documentary Planet Earth on monitor. Normally, both parts of the study took place the same day, but some had the MR scan the following day after behavioral testing due to scheduling preferences.

As a part of the MR scan, potential downsides to participation included discomfort of sound and time duration of MR scan, and potential incidental findings. All data was screened by a trained radiologist and any participant showing abnormalities would be contacted for subsequent clinical testing.

Behavioral testing

Behavioral testing consisted of handedness measurements, audiogram measurements and a behavioral oddball test. Handedness test was assessed using the Edinburgh Handedness scale (Oldfield, 1971) (See Appendix A), a computerized software audiogram tested the hearing acuity of participants and the behavioral oddball test assessed discrimination ability via a computerized test developed and ran using E-prime (Version 2.0).

The Edinburgh test measures handedness by the value of hand preference for 12 different items containing a description of a different daily activities. Each item gave either a positive score of + 40 for right hand preference or -40 for left hand preference. If preference was so strong for one hand that that the participant would never consider using other hand for a particular task, this was indicated by checking the box for that hand twice (+80). The scores were calculated and produced a score ranging from – 100 (exclusive left hand dominance) to + 100 (exclusively right hand dominance). A score of between – 40 to - 100 indicated left hand dominance and a score between + 40 to + 100 indicated right hand dominance (Oldfield, 1971). Although some reiterations of the inventory has been show to increase its efficacy (Milenkovic & Dragovic, 2013), the instrument has been widely used in research and has shown been shown to be a reliable measure of handedness assessment (McMeekan & Lishman, 1975; Williams, 1991). The inclusion criteria was + 40 and above.

For measuring hearing levels, a computerized audiogram was used. The audiogram software used was Oscilla AudioConsole (version 2.4.3) developed by Inmedico. The equipment used for measuring hearing levels consisted of a computer and a pair of sound isolating headphones with a response trigger connected, type Oscilla USB 300 developed by Inmedico A/S. The audiogram presented participants with the frequencies 250hz, 500hz, 1000hz, 2000hz and 3000hz at decibel levels -10, -5, 0, 5, 10, 15, 20 and 25. Every combination of frequency and decibel was presented. When participant heard a sound, they were instructed to press the response button. The subsequent scores represented what sounds participants could hear at least 50% of the time. Audiogram screening is well documented and has shown to accurately assess ability to hear (Walker, 2013).

To test and measure behavioral auditory discrimination ability a computer administered oddball test was used. In the experiment, participants were presented with 1976Hz sinusoidal baseline tones. The tone was identical to the standard tone used in the $_{1}$H-fMRS experimental protocol. The experiment was developed and presented in the software E-prime (version 2.0) on a laboratory computer. The frequency parameters (increments of change in percentage) used for the experiment have been found to adequately test discrimination ability (Baldeweg et al., 1999). The deviant stimuli were 2006hz, 2035hz, 2094hz and 2154hz. The ratio of deviant stimuli was measured as 80% standard tones and 20% deviant tones and the total amount of stimuli used was 500, where each deviant was presented 25 times in a total of 8 minutes test time. The interstimulus interval was set to 1000 ms and the stimulus lasted 75 ms with a 5ms rise and 5ms fall. The 75ms stimulus was

presented within a 100ms window to avoid clipping of the sound. The stimulus onset asynchronicity (SOA) was 1100. The total amount of deviants are within the limits of statistically testing discrimination ability (Cohen & Polich, 1997; Duncan et al., 2009). Sound volume was the same for each participant and was reported to be comfortable by participants. The testing was divided into a test run lasting 1 minute to allow participants to understand the task. Participant were instructed to respond to any deviation to the train of standard stimuli by pressing the ENTER key on the right side of the keyboard. Responses were recorded within the 1000 ms ITI between stimuli. Accuracy and reaction time for responses were recorded for both deviant and standards. During stimulus presentation, the screen remained black with centered white cross.

Measurements of age, sex and nationality were also recorded, but was not included in any analysis.

Auditory oddball stimulation during $_1$H-fMRS

The oddball paradigm was developed and presented using E-prime 2.0 Standard (Psychology Software Tools, Pittsburgh, PA). A total of 3400 stimuli were presented, where 80% were standard and 20% were deviants. The standard stimuli consisted of sinusoidal tones at a frequency of 1976 hertz which corresponds to the key of B in the Western musical denotation. The deviant stimuli consisted of sinusoidal tones at a frequency of 1319 hertz corresponding to the key of E. The frequencies were selected based on preliminary testing using EEG in combination with sound recordings of the MR scanner during an $_1$H-fMRS sequence. When developing the stimuli certain factors were taken into consideration. The sound frequency spectrum of the scanner noise was analyzed using a MATLAB (R2018a) script and the tones for the paradigm were selected based on: 1) Where the least dominant frequency range was for the scanner noise (e.g. the highest decibel of frequencies), 2) frequencies which did not overlap in terms of harmonic scales, so that the deviant and standard would not be perceived as a part of a harmonic and so that the deviant and the scanner noise would harmonically resonate with each other, 3) as close to western scale tones as possible. The EEG test runs were performed in order to see if any MMN could elicited under an artificial scanner acoustic environment. These were preliminary measures obtained by using the researchers themselves as subjects. The time duration of the tones was selected in accordance to guidelines outlining the optimal parameters for detection of MMN in EEG oddball studies (Duncan et al., 2009). All tones were 100ms, with 10ms rise and 10ms fall.

The stimuli were developed using MATLAB (R2018a). The tones were presented in a pseudo-random manner in order to avoid two deviants occurring after one another. The order was generated by an in house developed MATLAB (R2018a) algorithm which calculated the optimal deviant presentation order and interstimulus interval (ITI) for the given standard/deviant ratio in regard to the $_1$H-fMRS sequence, to ensure that the distribution of the deviant onsets was optimal with regard to the sampling the $_1$H-fMRS signal at multiple points of the acquisition. The algorithm calculated a range of different ITI times, where 220ms was deemed adequate considering acquisition and total scan time. Each 100ms stimulus was presented in a 150ms window. The presentation window in the software had to be set to 150ms to avoid sound clipping. This resulted in a 370ms stimulus onset asynchronicity (SOA). Which is the measurement of time from stimulus onset to the onset of the next stimulus. The total duration of stimuli presentation was 20 minutes. The participants were instructed to ignore the stimuli and watch the video being shown.

MR sequence and parameters

In order to test the main hypothesis, $_1$H-fMRS was used, allowing the measurement of glutamate and glutamine changes in the brain. This index is referred to as the Glx index and is a measurement of glutamate + glutamine (de Graaf, 2007). This measurement is often made in reference to some other abundant molecule in the brain. For this experiment a $_1$H-fMRS was used, which targets hydrogen atoms and allows for the indexing of glutamate and glutamine (Lei et al., 2014). A quantitative measurement Glx can be assessed by quantifying the signal relative to an water unsuppressed signal.

All imaging and spectroscopy data were collected using a 3T GE 750 Discovery Scanner produced by GE healthcare (General electric, Milwaukee, USA) with an 8 channel standard head coil produced by Invivo (Invivo corp., Gainsville, Florida, USA). These data were acquired by trained radiographs affiliated with the research group "Bergen fMRI Group".

Structural images were collected by first applying a 3-plane localizer sequence (2D spin Echo, TE = 80ms, FOV = 28mm, slice thickness = 10mm, slice spacing = 5mm), then a 3D T1 weighted fast spoiled gradient sequence (number of slices = 192, slice thickness 1.0mm, repetition time (TR) = 6.9ms, echo time = 2.95ms, FOV =256 x 256mm^2 , flip angle = 12 degrees, matrix = 256 x 192. A 24x28x20 mm^3 voxel was placed in the transverse temporal gyrus (Heschl's gyrus) in order to collect spectroscopy data from the auditory cortex.

A reference spectrum was also collected. A heart monitor was also used to collect data regarding the heart rate of the participants. Although MMN and heart rate changes have not been directly correlated, research has indicated that the presentation of a deviant stimulus is associated with a deacceleration of heart rate round 3-4 seconds after stimulus onset, likely reflecting an involuntary orienting response (Lyytinen et al., 1992). Heart rate has also been shown to impact BOLD responses in resting state fMRI research (Chang et al., 2009) so it was also taken as a control measure.

The spectral data was collected using a MEGA-PRESS (MEshcher-GArwood Point RESolved Spectroscopy) sequence (TE = 60ms, TR = 1500ms). This sequence has shown to reliably measure glutamate and glutamine (Glx), but at the same time assessing GABA, resulting in a good compromise between assessing these metabolites (van Veenendaal et al., 2018). The acquisition time was 20 minutes consisting 800 spectral frames. The MEGA-PRESS sequence was used to collect spectra in groups of six spectral frames, where the frames were collected with water suppressed MEGA-editing refocus pulse on (ON) and one off (OFF), which was followed by a third spectral frame without editing pulse and without water suppression (REF), then the next two frames in reverse order of the first two, OFF and ON and a final REF. The sequence went as follows: ON – OFF – REF – OFF – ON – REF (See Appendix B). The REF spectra were collected but was not needed for final analysis. The acquisition parameters were developed as a part of an earlier study investigating both BOLD, Glx and GABA (Dwyer, 2019).

Spectral analysis

The acquired spectra were first sorted using an in-house developed custom MATLAB (R2018a) algorithm based on condition (standard/deviant) and onset relative to the most recent stimulus of the given type. Given the ISI, it was possible for one acquisition to be in several bins (e.g., onset 0 ms after most recent standard and 700 ms after most recent deviant). Spectral peaks were calculated using Gannet (version 3.0) running in MATLAB (R2018a). Only water suppressed spectra were used for analysis. The raw MRS data was segmented into bins before spectral analysis. The in-house MATLAB (R2018a) script divided the conditions, standard or deviant, into eight bins for each condition. This was done by using a sliding window average. The times were calculated based on when the target sound (standard or deviant) was last presented. Thus, bins for 0ms, 100ms, 200ms, 300ms all represent one stimulus onset which was either a standard or a deviant occurring before an acquisition. Whereas bins 400ms, 500ms, 600ms and 700ms included more than one stimulus type. For

instance, if a deviant occurred and the spectra was collected 700ms after this deviant onset, there would be at least one standard within this deviant bin. This way of sorting out the data was deemed optimal considering MRS acquisition timing and oddball paradigm parameters. This however also resulted in deviants occurring more frequently in the later time bins due to the probability of a standards occurring after deviant (80%) vs deviants occurring after standards (20%). The bins consisted of data collected during ON and OFF acquisitions.

Statistical analysis

The MRS data was analyzed using two-way repeated measures ANOVA, with Glx level as the dependent variable. Two factors were included: Condition (standard/deviant) and Time ($_1$H-fMRS acquisition onset relative to stimulus onset: 0ms, 100ms, 200ms, 300ms, 400ms, 500ms, 600ms and 700ms). The same analysis was also performed for GABA data. As an explorative analysis, behavioral data was analyzed using correlation and regression analysis in order to investigate a potential relationship between performance on auditory testing and behavioral oddball deviance detection. A repeated measure ANOVA was also used in order to investigate if sensitivity to deviant stimuli in the behavioral paradigm was different between deviant types.

Exploration of the Glx data revealed three subjects as outliers, leaving N=11 for the statistical analysis. For removing outliers, the SPSS box plot function under explorative descriptive analysis was used. This function allows the researcher to visually inspect the data and detect any outliers. Outliers are defined as lying outside 1.5 of the upper or lower hinges of the interquartile range of the data. Extreme outliers are defined as lying 3 times outside this range (Parke, 2013). Several methods have been proposed in order to remedy some of the effect that outliers can have on the data. These measures include checking the data for error (mistyping scores), transforming data and simply adjusting the raw score of the outlier to be one unit smaller or larger than the next extreme score in the distribution (Tabachnick & Fidell, 2013). However, as Tabachnick and Fidell (2013) point out, the latter method is only relevant one the scores are somewhat arbitrarily given, such as measurements of construct via self-reporting, which does not apply to the current case since the scores represent quantitative measures from a spectrum of metabolites. Attempts of transforming the data were made, but did not rectify the impact of the outliers, so deletion was deemed a justifiable option. The last participant was not included because of an apparent technical error resulting in the inability to calculate spectral data. The source of the technical issue is not known. A Shapiro-Wilk's analysis was revealed to be significant before removing outliers, indicating that the data was

not normally distributed, this result persisted after data transformation. However, after outliers were removed, the Shapiro-Wilk's test revealed to be non-significant, indicating that the data met the assumption of normality.

Upon inspection, one outlier was removed for the analysis of the GABA data. By removing the outlier, the data met the assumption of normality as indicated by a non-significant Shapiro-Wilks test.

Results

Analysis of behavioral data

Handedness data was calculated by the following formula: (Right hand data – left hand data)/(right hand data + left hand data) * 100. This formula yielded a laterality quotient (LQ) which indicated the degree of right or left hand dominance participants had (Caplan & Mendoza, 2011). These measurements were not used in subsequent analysis and served only as a control measure. The test revealed that all participants were right hand dominant (M = 78.3, SD = 19.4).

The hearing test measurements were written down and plotted into an excel sheet were an auditory acuity index was calculated by averaging scores from each ear together. A total auditory acuity score and an auditory acuity score for sounds at 2000hz was calculated for each participant. The indices were labelled "TotalAuditoryAcuity" and "2000hzAuditoryAcuity" respectively. Normal hearing was defined as perceiving sounds at 20 decibels and below (Hugdahl et al., 2009). The test lasted around 5 minutes. All participants included in the inferential analysis showed to be within the range of normal hearing (M = -2,27, SD = 4.17).

Data from the Oddball test was imported to Excel where it was sorted, and discrimination ability indices were calculated. The index of discrimination ability was d' (Dee-prime). This is widely used in detection theory and regarded as an adequate statistic for assessing discrimination ability (Macmillan & Creelman, 2004). The index is calculated based on successful deviation detection. For the behavioral oddball test, four outcomes could be assessed during experimentation. Participants were expected to respond by pressing a key to deviants and remain passive in response to a standard. These four options can be explained as: 1) a true positive, which is correctly pressing the key in response to a deviant. 2) A false negative, which incorrectly not pressing the key in response to a deviant. 3) A true negative, which is not pressing the key in response to a standard and 4) a false negative, which is incorrectly pressing the key in response to a standard. The words "positive" and "negative" in

this context simply indicates the occurrence of an action (positive) and omission of an action (negative). The index is calculated by first calculating the hit rates (H) and false positive rates (F). The hit rates are calculated as follows H = True Positives/Total Deviant Trials. The false positive rate is calculated as follows F= False Positives/Total Standard Trials. The H and F are regarded as estimated conditional probabilities of stimuli detection (Macmillan & Creelman, 2004). These scores are then converted to Z scores: z(H) and z(F). These scores represent standard deviations, where a score of .5 is converted to a Z score of 0. The *d'* is calculated by the following formula *d'* = z(H)-z(F).

The *d'* measure contains both the ability to detect deviants and discriminate them from a standard stimulus, which means that the score will change according to correct responses and false responses, reducing potential biases of either over or under responding to the stimuli (Macmillan & Creelman, 2004). If the calculated H or F is 1 or 0 a problem arises, where transforming these rates into scores results in a theoretical infinite Z score. If a H or F score was not possible to transform to a Z score, both the H and F for this participant was adjusted by adding 0.5 to both the true positive and the false positive score, and by adding 1 to the deviant trials and standard trials. This approach has been found to adequately resolve the problem of 1 and 0 scores in *d'* calculation (Stanislaw & Todorov, 1999). A *d'* index was calculated for each of deviants, 2006hz, 2035hz, 2094hz and 2154hz, and a total *d'* containing all the beforementioned deviants. This yielded five *d'* indices: , " 2006 *d'* ", "2035*d'* ", " 2094 *d'* " and " 2154 *d'* " and " Overall *d'* ".

Analysis of behavioral data consisted of N = 11, which had four missing participants. Explorative analysis revealed a Shapiro Wilk's test for normality as non-significant, indicating that the data met the assumption of normality. Although Boxplot methods revealed some data as potential outliers, the Shapiro-Wilk's test did not reach significance. This data was therefore included. The data was analyzed using a correlation analysis in order to investigate any relationship between auditory acuity and behavioral discrimination *d'*. Subsequent regression analysis was also planned in order to investigate this relationship further. The four missing data was due to a technical error. And potential recollection of data was not possible due to the Covid-19 pandemic.

MR analysis results

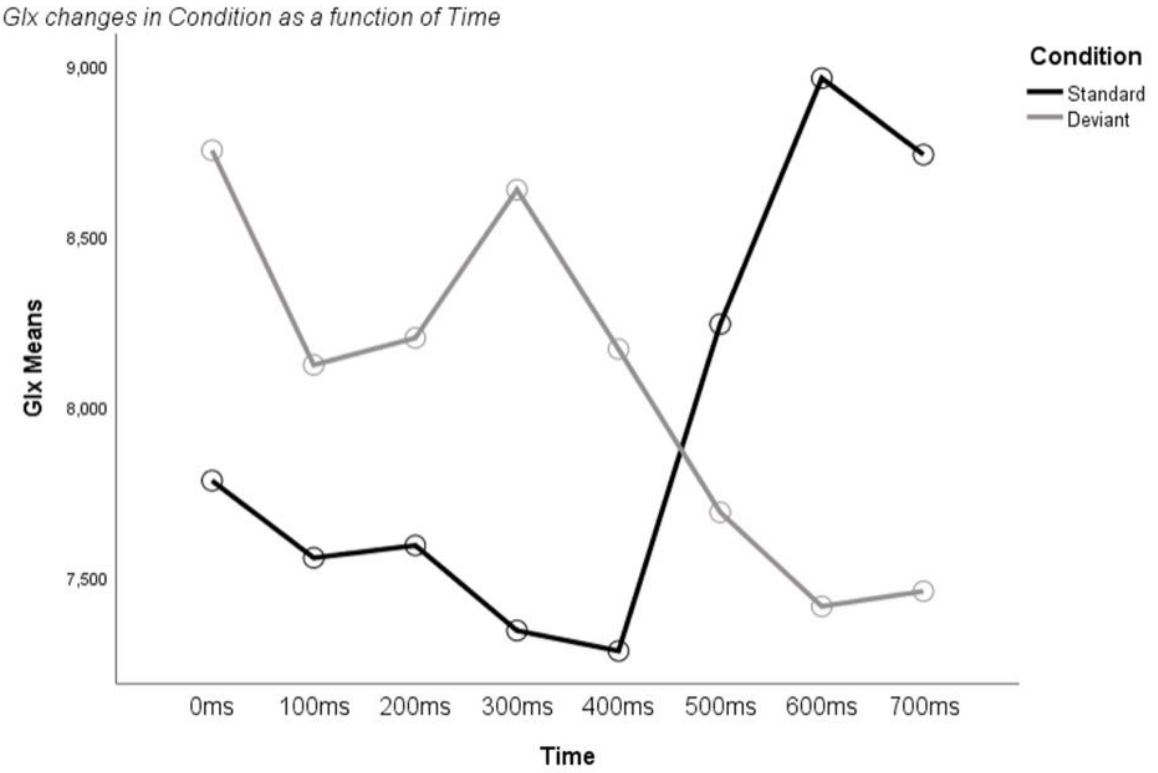
For the sake of transparency, analysis of data with and without the outliers will be presented for this analysis.

Repeated measures ANOVA investigating the difference between the levels Condition and Time on Glx for the data including the outliers (N = 14) revealed no significant effects. The assumption of sphericity was not met, so a Greenhouse-Geisser correction was used. The interaction effect for Condition and Time was found to be non-significant $F(2, 29) = 2.06$, $p = .139$, $\eta p^2 = 0.13$.The main effect for the Condition variable was found to be non-significant $F(1, 13) = 0.81$, $p = .383$, $\eta p^2 = 0.06$. And lastly, the main effect for the Time variable was found to be non-significant $F(2, 26) = 1.54$, $p = .232$, $= 0.1$.

Repeated measures ANOVA with the outliers excluded (N = 11) investigating the difference between the levels of Condition and Time on the dependent variable Glx revealed a significant interaction effect between Condition and time $F(2, 21) = 3.59$, $p = .044$, $\eta p^2 = 0.26$. No main effects for Condition nor Time was found. The repeated measures ANOVA revealed a non-significant difference between levels for Condition $F(1, 10) = 0.845$, $p = .380$, $\eta p^2 = 0.078$ and a non-significant difference between the levels in Time $F(2, 25) = 0.787$, $p = .492$, $\eta p^2 = 0.073$. Post-hoc analysis was used to further investigate the interaction effects found for Conditon and Time.

To further investigate the interaction effects between Condition and Time, a pairwise comparison was made. The pairwise t-test was used to investigate the difference between the standard and the deviant at each time point. The post hoc analysis revealed that there was a significant increase in Glx to Deviants ($M = 8.63$, $SD = 1.9$) relative to Standards ($M = 7.34$, $SD = 0.87$) at 300ms, $p = .023$. There was also a significant increase in Deviants ($M = 8.16$, $SD = 1.14$) relative to Standards ($M = 7.28$, $SD = 1.02$) at 400ms, $p = .015$. Lastly, there was a significant increase in Glx for Standards ($M = 8.74.$, $SD = 1.86$) relative to Deviants ($M =$ 7.45.63, $SD = 1.72$) at 700ms, $p = .038$. Figure 1 shows Condition over Time.

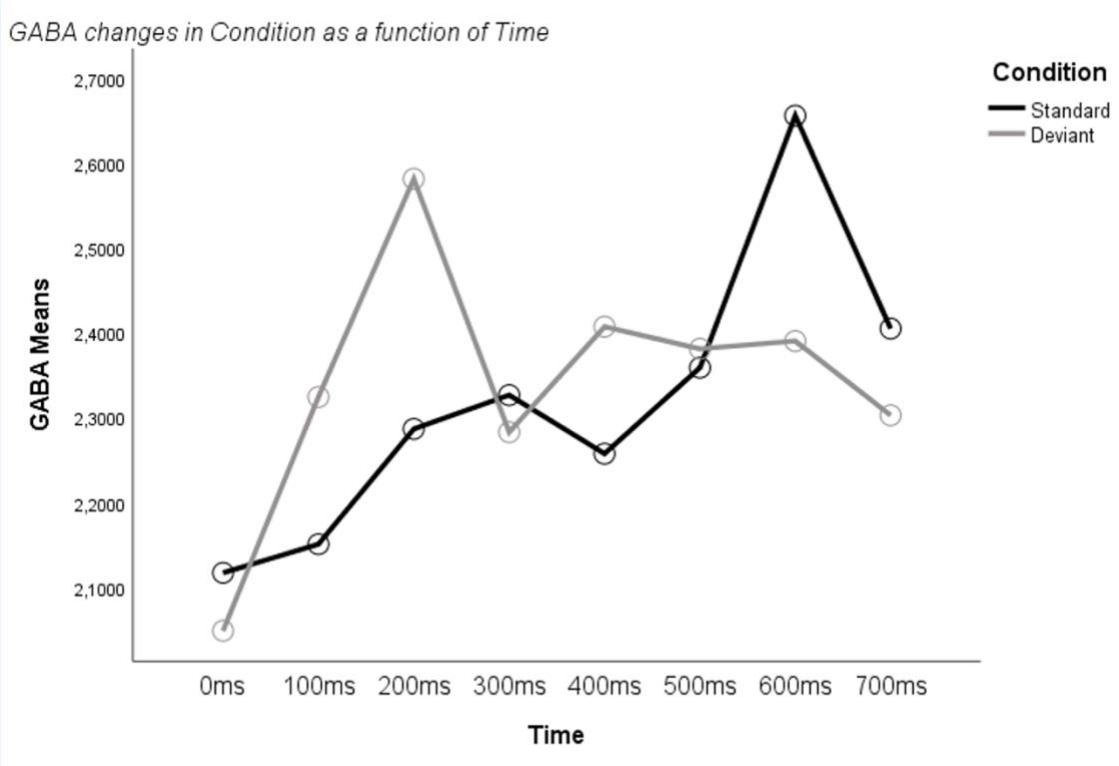
Figure 1



Note. The mean Glx scores for Standard and Deviant (Y axis) across eight times points of acquisition (X axis).

A repeated measures ANOVA with outliers excluded (N = 13) investigating the difference between Condition and Time on the dependent variable GABA. The assumption of sphericity was not met, so a Greenhouse-Geisser correction was used. The analysis revealed a significant main effect of Time $F(3, 35) = 3.26$, $p = .034$, $\eta p^2 = .214$. No main effect for Condition was found. No interaction effect was found for Time and Condition. Post hoc analysis using pairwise comparison and a Bonferroni correction was performed to further investigate the main effect of Time. The post-analysis revealed that 0ms ($M = 2.08$, $SD = 1.01$) was significantly lower than 200ms ($M = 2.43$, $SD = 1.19$), $p = .029$. The post hoc also revealed that 100ms ($M = 2.23$, $SD = 1.07$) was significantly lower than 200ms ($M = 2.43$, $SD = 1.19$), $p = .021$. It was also found that 0ms ($M = 2.08$, $SD = 1.01$) was significantly lower than 600ms ($M = 2.52$, $SD = 1.31$), $p = .001$. And lastly, 100ms ($M = 2.23$, $SD = 1.07$) was significantly lower than 600ms ($M = 2.52$, $SD = 1.31$), $p = .022$. Figure 2 shows the increase in GABA over Time.

Figure 2



Note. The changes in the GABA response to both Deviant and Standard stimuli. The time stamps represent $_1$H-fMRS acquisitions occurring after stimulus onset.

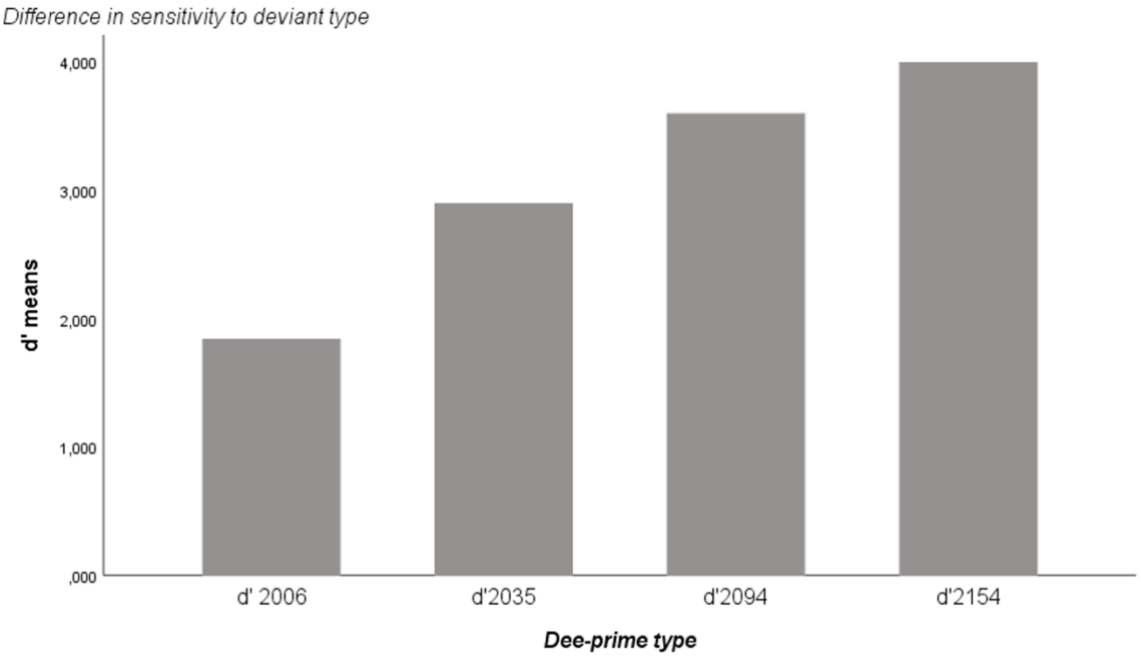
Explorative Analysis

Correlation analysis revealed no correlation between performance on Overall *d'* and TotalAuditoryAcuity ($r(20) = .05$, $p = .874$). Further correlation analysis revealed that there was no significant correlation between ability to detect the smallest increments of deviants 2000 *d'* and TotalAuditoryAcuity ($r(20) = -.23$, $p = .477$). There was no significant correlation between Overall *d'* and 2000hzAudtoryAcuity ($r(20) = .252$, $p = .453$). And lastly there was no correlation between 2000 *d'* and 2000hzAudtoryAcuity ($r(20) = .090$, $p = .792$). Further, regression analysis revealed no significant relationship between TotalAuditoryAcuity and Overall *d'* $\beta = .0076$, $t(1,20) = .026$, $p = .874$. Performance the auditory test could not explain the variance behavioral deviance detection $R^2 = .002$. The 2000hzAuditoryAcuity as a predictor for the variance in the Overall *d'* was also found to be non-significant $\beta = .046$, $t(1,20) = .614$, $p = .453$. Where this model could only account for 6% of the variance of overall behavioral deviance detection $R^2 = .064$. Lastly, 2000hzAudtoryAcuity could not significantly account for the variance in 2000 *d'* $\beta = .021$, $t(1,20) = .073$, $p = .792$. The model

could only account for 0.8% of the variance in the smallest deviant $R^2 = .008$.

A repeated measures ANOVA was performed in order to investigate differences in the ability to discriminate between the different increments of deviants. The assumption of sphericity was found to be met by running a Mauchly's test for sphericity. The sphericity assumed results indicated that there was an overall significant difference between the *d'* scores, $F(3,30) = 32.37$, $p < .001$. The overall effect size revealed that 76% of the variation in error scores could be account for by the difference between the ability to detect deviants, $\eta p^2 = .764$. A Bonferroni post-hoc analysis was used to further investigate the difference between the particular deviant types. Pairwise comparisons revealed five significant differences among the deviants, where the largest difference was for 2006 *d'* and 2154 *d'*, mean difference = 2.15, $p <.001$, 95% Cl [-3.25, - 1.06]. There was a difference between deviant 2006 *d'* and 2094 *d'*, and between 2006 *d'* and 2035 *d'*, mean difference = 1.75, $p < .001$, 95% Cl [-2.44, - 1.07], mean difference = 1.05, $p = .009$, 95% Cl [-1.85, - 0.26], respectively. There were also significant differences between 2035 *d'* and 2094 *d'*, and between 2035 *d'* and 2154 *d'*, mean difference = 0.70, $p = .007$,95% Cl [-1.21, - 0.188], mean difference = 1.09, $p = .004$, 95% Cl [-1.84, - 0.35], respectively. There was however no significant difference between discrimination between the two largest deviants. The finding indicate that deviance detection was lower for smallest deviants ($M = 1.837$, $SD = 0.227$) and increased as a function of difference from the baseline stimulus as seen in figure 3. The second smallest deviant ($M = 2.895$, $SD = 0.245$) was detected more often than the smallest, but lesser than the second largest ($M = 3.596$, $SD = 0.217$) and largest ($M = 3.994$, $SD = 0.299$). The two largest deviants had equal probability of being detected.

Figure 3



Note. This figure demonstrates the mean differences in sensitivity for detecting the different increments of deviation. This illustrates that detection increased as a function of increasing difference between standard and deviant.

Discussion

The results from the data with excluded outliers revealed no main effect of Time, indicating that Glx levels did not increase in response to any stimulus onset. No main effect of Condition indicated that there was no significant difference between standard and deviant in general. However, the interaction revealed a significant effect, and subsequent post hoc analysis revealed that there was an increase in Glx for deviants 300ms and 400ms after stimulus onset relative to standards at the same time points. And furthermore, there was an increase in Glx after the onset of standards relative to deviant occurring at 600ms. It should also be noted that the no correction measure was used for the post hoc analysis, which could potential yield a higher rate of false positives when running multiple t-test (Tabachnick & Fidell, 2013). The comparisons made were deemed reasonable, where a deviant was measured against standards at the same time point. The aim of the post hoc analysis was to see if any meaningful differences could be observed.

The exclusion of outliers was argued to be the only option if the assumption of normality was to be met. Specifically for repeated measures ANOVA, small sample sizes with normality have been found to be especially important, where analysis for sample sizes up

towards N = 50 have been found to suffer from non-normal data (Oberfeld & Franke, 2013). Although the initial sample size was quite small, removing outliers yielded a sample size of N = 11. This is found to be the typical sample size in ^{1}H-fMRS studies employing various paradigm that have yielded robust findings of Glx measures (Mullins, 2018). Although removal of outliers has been shown to inflate the chances of false positives (Type 1 error) (Bakker & Wicherts, 2014a), research investigating the effects of outlier removal in psychological research have shown that removing outliers does not significantly impact the mean p value or quality of research (Bakker & Wicherts, 2014b). However, as argued by the authors, some articles may not report the removal of outliers, which may contaminate the results. The articles used to investigate the effect of outlier removal also had quite high sample sizes in contrast to the present study, where the mean sample size of articles reporting outlier removal was N = 119, and M = 82.

Main effects of Glx

A potential source of the non-significant finding for either Condition and Time might be explained by a point made by Mullins (2018), which suggested that repeating stimuli may lead to repetition suppression, which suppresses glutamate activity over the entire course of the experiment. This point was made in light of studies using blocks of stimulation with rest blocks in between. For instance, Taylor et al. (2015) found an initial increase in glutamate in response to a Stroop task block lasting 4 minutes. However, after a recovery block of 4 minutes, the second Stroop block failed reach significant glutamate levels relative to baseline measures. Another study by Ip et al. (2017) investigated glutamate and BOLD responses to visual stimulation in 64 second alternating blocks of stimulation and rest. A significant increase in glutamate was found in response to visual stimulation, however, this response decreased steadily after the first rest block, indicating a repetition suppression over the course of the entire experiment (Mullins, 2018). Considering the rapid and slow nature of glutamate responses in neural microcircuits (Askew & Metherate, 2016), there seem to be a decrease in the response of glutamate even after long periods of rest, even if participants had their eyes closed during rest blocks (Ip et al., 2017). This may be a possible explanation of why there was no significant difference between conditions or time. If one could track the glutamate levels across the entirety of the acquisition block (20 minutes in this case), perhaps this trend would be apparent. However, this is only speculation. In order to conduct the oddball paradigm, fMRS acquisition and experimental stimulation ran independently, and an E-prime script was used to track trigger pulses from the MR. These timestamps were then used to

calculate the timing. Sadly, due to the constraints on the experimental protocol, around four to five stimulus presentation would occur between each acquisition (370ms SOA and TR = 1500ms) and binning the data in order to increase S/N ratio, tracking the change over time was not feasible.

Another consideration is noise from the scanner. Scanner noise is a common problem among auditory fMRI research (Peelle, 2014) Research on the effect of scanner noise on the BOLD signal has revealed a significant decrease in signals retrieved from auditory cortices, most likely due an increase in baseline activation in this area (Gaab et al., 2007), leading to a compromised dynamic range which would impact the ability to discriminate between stimuli of the auditory cortex (Peelle, 2014). The effect was especially pronounced in Heschl's gyrus, with moderate effects on secondary and higher cortical areas. Nonlinear interaction between stimuli and BOLD signals due to scanner noise has also been reported (Langers et al., 2005; Talavage & Edmister, 2004), where these interactions were more complex when tone frequencies were more similar to scanner frequencies (Langers et al., 2005). The effects of scanner noise may prohibit the assessment of linear measures of cortical activity due to its non-additive effect on measurements (Talavage & Edmister, 2004). This may convolute the ability to determine if the signal retrieved with the MR arises from the desired auditory stimulation or undesired scanner noise sounds (Talavage & Edmister, 2004). Although Langers et al. (2005) pointed out that the effect of the scanner was less pronounced for stimulus frequencies more separate from the scanner frequencies, the scanner still introduced a confound. Reliable results have however still been obtained with auditory paradigms, by introducing silent periods of stimulation and other methods of circumventing the noise issue (Hall et al., 2000; Peelle, 2014; Shah et al., 1999). These considerations were made for the hemodynamic response underlying the BOLD signal, but it seems reasonable to infer that these problems would ring true to a glutamate response to auditory stimulus. Although some frequency overlap was taken into consideration when developing the auditory stimulus, as Langer et al. (2005) points out, this does not necessarily eliminate the issue of scanner noise. There may however been less confounds from the scanner noise due to $_1$H-fMRS sequences being considerably quieter than fMRI sequences. Methodologies used in fMRI research to circumvent these issues will hopefully inspire similar solutions in $_1$H-fMRS $_1$H-fMRS research.

Another explanation for why the no significant increase in Glx was found may have to do with the region of interest. Though it is found that the left hemishphere is general

dominant in auditory processing (Devlin et al., 2003), research has found that right the hemisphere shows a dominant MMN signal to frequency-, intensity- and duration deviants (Paavilainen et al., 1991). Research has also shown that left the hemisphere may be more sensitive to temporal aspects of auditory stimuli, where as the right hemisphere maybe more sensitive to spectral qualities of sound, such as frequency (Zatorre & Belin, 2001). Moreover, PET studies tracking cerebral blood flow as an index of neural activitiy have found that the right hemisphere seem to be more active during processing of musical stimulation (tones), whereas the left has shown dominance to language features (Hugdahl et al., 1999). It's also been argued that right hemispheric specialization of auditory spectral features and left specialization to temporal features also comes as a consequent that right auditory cortices show a more clear tonotopic organization, where as left hemisphere shows less (Liégeois-Chauvel et al., 2001). Therefore, this functional and physical asymmetry may help explain the failure to measure glutamate increases to auditory stimulation in this study.

Sex differences in MMN measures have been found for younger populations, such as the one studied here, where research indicated different location intensities in the MMN signal for males and females. Specifically, females showed a larger intensity in the MMN in frontal regions, where as men had stronger MMN signal from the temporal regions (Tsolaki et al., 2015). This may have implications for this particular study, considering that the initial sample was two thirds female, and after removing outliers females still roughly constituted two thirds of the participants included in the analysis. The area under investigation was in the temporal region, so this may have impacted measurements. Although these difference may not suffice to explain all the whole picture, together with the other considerations mentioned here, it may play a part of the failure to detect glutamate changes.

Interaction effects of Glx

Considering that the evolvement of the glutamate response in the brain is still not well understood, one could argue that the indexing of prediction error by the Glx measurement does not necessarily equate to the time locked responses found in EEG and MEG research. Regardless of no main effect found in this study, the results from the interaction effects are still interesting. Traditionally, a prediction error index as MMN could be detected between 100 to 200ms after stimulus onset (Näätänen & Winkler, 1999). More recent interpretations of the prediction error have conceptualized it as consisting of a sensorial part peaking within the N1 range, from 105ms to 125ms and a later cognitive component which consist of a comparator mechanism occurring at 170ms to 200ms (Maess et al., 2007). Studies have also

found that MMN latency changes as a function of frequency difference between standard and deviant stimuli, where the MMN peak latency decreased monotonically from 180ms to 110ms as the difference between standard and deviants increased (Tiitinen et al., 1994). These findings are speculated to come from N1 contamination of the "true" MMN signal, but have also been argued to support the notion that the MMN index is actually fresh afferents tuned to the deviant stimulus specific characteristics which become activated, but are delayed due to lateral inhibition from neighboring neurons responding to the standard stimulus (May & Tiitinen, 2010). Given the present results, the finding of higher glutamate levels 300ms and 400ms after stimulus onset would at first glance not fit into the time frame presented above. More spectrally rich deviants, such as tones with missing fundamental have been found to elicit a later latency MMN up to 280ms after deviant onset (Winkler et al., 1998). These were however for more complex tones, whereas the current study employed simple pure tones. One potential explanation for the increased Glx to deviants at these time points in the current study might be that the scanner noise imposed on the auditory stimulus, where pure tones coincidently harmonized with the scanner noise, and thus were processed as a more complex tone by participants. As mentioned previously, scanner noise may impact auditory stimulation frequencies in a unexpected fashion (Langers et al., 2005). Although this does not necessarily warrant why the glutamate response was measured at 300ms and 400ms, it shows the variation in latencies which can occur when frequency parameters impacted. Moreover, earlier studies investigating the effects of noise on ERP elicitation has found an increase in latency of MMN, N1 and P300 when auditory stimulation was given with various degrees of broadband masking noise (Brett A. et al., 1999; Muller-Gass et al., 2001; Whiting et al., 1998). Where broadband noise was found to increase latencies of MMN up to 122ms (Brett A. et al., 1999). Although these studies found MMN signals within the range of 100 to 250ms, the example still highlights the potential effects of noise on prediction error elicitation.

Given the results outlined by Mullins (2008) based on findings by Apšvalka et al., (2015) and (Lally et al., 2014), a glutamate peak acquired 300ms – 1000ms after stimulus are within the time frame collected in this present study. It should be noted that Apšvalka et al. (2015) sampled a water suppressed spectrum on average every 300ms after stimulus onset, with 3 seconds between acquisitions these acquisitions, and a water unsuppressed spectrum every 1800ms after stimulus onset, which revealed a change in glutamate between these periods of between 11% to 13%. The researchers further argued that because of the change in such a short time period (within 3 seconds), it may indeed be the movement of glutamate from synapse to

extracellular space. Furthermore, Lally et al., (2014) found increases in glutamate 950 to 1150 seconds after stimulus onset. Although neither of these studies used oddballs and both used visual stimulation, Apšvalka et al., (2015) used novel stimuli to induce glutamate increases among standard stimuli. The aim was to induce repetition suppression, and thereby see if novel stimuli would increase glutamate. Lally et al. (2014) used unfamiliar images e.g abstract images, contrasted with familiar images as experimental stimulation. By virtue of both these paradigms using unexpected stimuli (novel and abstract) they give some value to the direction of prediction errors induced by oddballs. Especially the former study aiming to investigate the effects repetition suppression, an important function in producing the prediction error signal (May & Tiitinen, 2010). The increase in glutamate here may be the suppression of the prediction hierarchy trying predict another deviant stimulus incoming. The suppression of pyramidal neurons happens through parvalbumin (PV) interneurons, which are activated through AMPA and NMDA receptors, which means that excitation in pyramidal neurons cause subsequent inhibition through excitation of inhibitory interneurons containing NMDA receptors (Gonzalez-Burgos & Lewis, 2012). This necessitates that glutamate is present to activate the interneurons. Perhaps the recurrent activation of interneurons in order to suppress the pyramidal cells tuned to the deviant tone is what caused this temporary spike in glutamate. In predictive processing terms, this would be a prediction descending down the hierarchy and suppressing the neurons tuned to the deviant stimulus in order to suppress a subsequent prediction error. This suppression would occur through an initial increase in glutamate in order to trigger a subsequent GABAergic neuron.

Alternatively, the findings by Lally et al., (2014) found increased gamma band activity between 50 to 250ms after stimulus onset, which was correlated with the later glutamate levels. This type of gamma band activity has also been found for repetition suppression paradigms, which used unexpected repetitions or omission as deviants, found increases in gamma band activity 300ms and 200-400ms after deviant onset, respectively (Todorovic et al., 2011). These authors argued that repetition suppression was modulated by top down prediction and conceptualized their increases in gamma band activity as prediction errors. This may indicate that what Lally et al., (2014) indexed was a prediction error, and the subsequent glutamate response which was associated with this gamma band increase could be argued to represent a type of prediction error. This can also be used to speculate that the unexpected stimulus used in the study by Apšvalka et al., (2015) which was associated with an increase in glutamate around 300ms after stimulus onset would have been found in the

study by Lally et al., (2014) had they measured earlier. These findings highlight the potential dynamic nature of glutamate in response to unexpected stimuli and implicate gamma band activity as a potential measure of this phenomenon. Indeed, proponents of the predictive processing framework have suggested that prediction error signals are conveyed via superficial glutamatergic pyramidal neuron in the gamma frequency range (Friston et al., 2016)

And recent suggestions that temporal cortical responses to smaller time courses appear in the lower cortical areas and longer time courses are responded to in higher cortical areas (Parr et al., 2018), which may indicate that the prediction error signal is not as dichotomous as previously thought. The MMN index has been mostly discussed in terms of temporal and frontal generators at otherwise fixed timepoints (Näätänen et al., 2007). Findings by Friston et al. (2017) further elucidates the potential for later MMN responses, where these researchers investigated the effects of local and global rule violation by manipulating lexical and contextual violation when reading. Here, they successfully found that MMN was elicited by local violation, whereas P300 was elicited by contextual violation. When looking at the interaction of global and local violation, the authors noted that there was an effect of local violation on global violation shown as an increase in MMN amplitude and the positive P300 amplitude, but not the other way around. This led the researchers to suggest that global violation indicated by P300 may be generated by the same sources as MMN. Although there were no "global" regularities explicit in the paradigm for this particular study, it illustrates that perhaps later prediction errors driven by glutamate change in areas associated with MMN generations, which may help explain the results of the current findings, that what was observed at 300ms and 400ms was in fact a prediction error generated to deviants, but that the nature of the pure tones was somewhat obscured by the acoustic environment, making the discrimination between otherwise simple tones appear more complex to the predictive hierarchy

Post hoc analysis also revealed a significant increase in Glx 700ms after standard sounds onset compared to deviants at the same timepoint. This finding might be somewhat confusing given the current paradigm and repetition suppression that happens for standard stimuli, however, when considering how the later bins were calculated, this makes sense. For a standard to be binned as 700ms, a standard had to be presented 700ms before acquisition. However, this would also mean that between standard presentation and acquisition, a deviant would appear. Meaning, that 370ms after the standard was presented, a 100ms deviant

appeared in the time window of 150ms. This would result in a deviant stimulus terminating at 510ms, and at 700ms an increase in glutamate was found. This may be indicative a prediction error response to the oddball. Considering that the 700ms acquisition happened 330ms after the deviant onset, this is similar to the responses found for 300ms and 400ms. However, this interpretation should be taken with caution given that the probability of a deviant following a standard was much rarer than a standard following a deviant. This resulted in a bias where bins containing 500, 600 and 700ms standards having much fewer acquisitions than the deviants occurring at the same time, which could have made some extreme scores more potent spectral analysis of the bins.

Although one can argue that the current Glx measurement may not constitute neurotransmission, e.g activity, but rather a resting level of glutamate and glutamine not necessarily involved in neurotransmission in response to stimulation. This may be possible given that the Glx index is the combined measurements of glutamine and glutamate. However, the use of longer echo times in the present study, 68ms, is argued to be more sensitive to the signals from glutamate moving from intracellular to extracellular compartments (Mullins, 2018).

It may also be the simple fact that the Glx measurement used in the current study could not detect the rapid changes in glutamate, and subsequently indexing prediction error as an increase in Glx may have different time scales due to the signal constituting both glutamate and glutamine, not truly reflecting the NMDA glutamate activity thought to drive the signal (Askew & Metherate, 2016).

Recent studies investigating the correlation between glutamate/glutamine levels and ratios, GABA and MMN found that lower levels of frontal glutamate and GABA were associated with diminished MMN among individuals with Schizophrenia, but not among controls (Rowland et al., 2016). The relationship between glutamate and GABA is tightly coupled through E/I balances (Askew & Metherate, 2016) and these functions help tune the cortical areas to specific stimulus characteristics, aiding in increasing signal to noise ratio in the cortex (Askew & Metherate, 2016; Hancock et al., 2017). Moreover, a recent study investigating glutamate levels in the hippocampus and temporal cortical areas found higher levels of glutamate were correlated with higher MMN amplitudes. These findings together paint a picture of E/I balances being crucial for prediction error generation, and glutamatergic pyramidal cells in conjunction with inhibitory GABAergic interneurons driving the prediction error signal (Batista-Brito et al., 2018) This may indicate that the increases found here are

indeed related to the generation of prediction error, however the GABA measurements found in the present study may help corroborate these claims given their role in these E/I circuits.

GABA

A measurement of GABA was also performed in order to gain a more complete picture of the prediction error phenomenon. The results showed a significant effect of Time on GABA levels. Post hoc analysis revealed an increasing trend of GABA levels from stimulus onset to 600ms. The trend revealed a significant increase from 0ms to 200ms and from 100ms to 200ms. This trend is strange seeing how an expected significant increase from 0ms to 100ms would be expected, but this was revealed to be non-significant. However, the initial increase in GABA is to 200ms may indicate the tight coupling between glutamate and GABA (E/I microcircuits) in the auditory cortex, and may also help elucidate the failure of finding a significant increase in Glutamate for the first 300ms after stimulus onset. When considering the rudimentary processes that glutamate and GABA serve, whereby pyramidal neurons using glutamate as a main excitatory neurotransmitter, which is heavily regulated by several types inhibitory GABAergic interneurons (Batista-Brito et al., 2018), these findings may be expected. The disfunction interneurons have been implicated in aetiology of Schizophrenia (Selten et al., 2018), where somatostatin (SOM) expressing inhibitory interneurons have been especially implicated in the generation of mismatch negativity (prediction error) (Hamm & Yuste, 2016). The tight coupling of excitation and inhibition through exctatory pyramidal and inhibitory pervalbumin interneurons allows neural circuits to fire in a cycle by cycle fashion, where any excitation of a pyramidal neurons is instantously counterbalanced by a inhibition proportionally four to five times larger than the excitation (Atallah & Scanziani, 2009). This may be the why an increase in GABA was found, but not in glutamate during the first 200ms. These quick acting balances have been found to allow excitatory post synaptic currents and inhibitory post synaptic currents to remain proportional despite large variations in gamma band amplitude. Although these measurements were done in CA3 of the hippocampus, similar post synaptic potentials, EPSP and IPSP have been linked to the generation of prediction errors in the auditory cortex (Askew & Metherate, 2016). Specifically, gamma fluctuations recorded during auditory stimulation most likely index quick depolarization and chlorine mediated hyperpolarization (EPSP and IPSC) of neural populations, where this network activity most likely reflect slow NMDA mediated EPSP's linked to prediction error generation (MMN) (Askew & Metherate, 2016). This may indicate

that the increase in GABA over time found here may underlie repetition suppression and lateral inhibition thought to serve the generation of prediction errors (May & Tiitinen, 2010).

The reason that the no difference in Glx between standard and deviants were found in the first 200ms, may be due to this inhibition, perhaps together with an already compromised baseline activity induced by scanner noise, the earlier EPSP (AMPA receptors mediated) may not have been strong enough to give a significant S/N ratio for the fMRS measurement, but the later EPSP (NMDA mediated) (Askew & Metherate, 2016) prediction error mechanisms may yielded a strong enough signal. Whereas both earlier IPSP and later IPSP releasing the EPSP gave a large enough response in general to detect with the fMRS. This timing fits well with the findings reviewed in the introduction, where later IPSPs were found to last for 200-300ms (Wehr & Zador, 2005), which may indicate that the findings in the present study suggested a release from the inhibitory later IPSP, causing an increase in glutamate, as indicated by the Glx at 300ms and 400ms. And more so, the increase to deviant stimulus relative to standard stimulus may indicate a prediction error elicitation. Although it was pointed out that this IPSP time course may only explain a small part of the prediction elicitation (Wehr & Zador, 2005). However, these interpretations are speculative at best.

The relative increase in GABA at around 600ms may also be explained by this, whereby the tight balancing of excitatory glutamate activity and GABA underlying the prediction error phenomenon was recorded inadvertently when bins collecting "Standard" stimuli contained a deviant occurring 230ms before the 600ms acquisition. The consideration above should however be taken with great caution due to the fact that no main effect for Condition was found for GABA, where one would expect a larger GABA response for the deviant, due to the large proportional relationship between excitation and inhibition during stimulation (Atallah & Scanziani, 2009).

It may also be that increases in GABA simply a result of the auditory cortex responding to auditory stimulation in general, and the increase found here is the consequence of normal inhibitory responses of PV neurons fine tuning micro circuitry allowing for more precise stimulus discrimination (Blackwell & Geffen, 2017).

Considering how the study was already underpowered given the estimated sample size of N = 30, and the removal of outliers due to extreme scores, and the failure to find significant main effects for the Glx scores, what can be definitive is that a general increase in glutamate to auditory was not found. Although the interaction effects yielded interesting results, they are too uncertain to be used to generate any new hypothesis and serve mainly as a way of perhaps

elucidating some of the complex nature and uncharted territory of the underlying mechanisms of prediction error. The main hypothesis of this study was explorative in nature, and the technique applied was a proof of principle. Although a large body of information served as a guide to what molecular underpinning prediction error may be, the uncertainty of both how glutamate evolves over time (Mullins, 2018) and the technical challenges of auditory stimulus in the context of an oddball paradigm with an fMRS MEGA-PRESS sequence limits the inferences which can be made from the current results. However, more participants are to be collected, which can perhaps make it more possible to detect increases in Glx to auditory stimulation.

Although previous studies have found increase in Glx to both visual/cognitive stimulation (Apšvalka et al., 2015; Lally et al., 2014; Woodcock et al., 2018), the indices collected are not necessarily direct measurements of glutamate mediated by excitatory neural activity linked to some cognitive construct or stimulation. This is however a problem with most techniques, such as localizing the origin of activity measured with EEG and MEG referred to as the inverse problem (Hämäläinen et al., 1993), and fMRI with not only the inferences made of neural activity from BOLD signals, but also the assumption of pure insertion, which asserts that a single cognitive construct can be inserted or probed without affecting other such constructs (Logothetis, 2008). Therefore, there may be similar problem pertaining to fMRS research. The Glx index measures both glutamate and glutamine, and based on TE timing, may be sensitive to different compartments of glutamate and glutamine within the brain(Mullins, 2018). Moreover, the sheer ubiquitous nature of glutamate and our still limited understanding of how the metabolic cycles of glutamine, glutamate and GABA unfold in the brain (Zhou & Danbolt, 2014) may all limit inferences made of cognitive constructs specifically pertaining to changes in Glx. Although this critique pertains to behavioral neuroscience in general, it seems appropriate considering the explorative nature of phenomenon under investigation, and even more so when considering the measurement technique with this particular experimental protocol.

Explorative findings

No significant relationship was found between performance on auditory measures and the behavioral oddball paradigm. Overall hearing acuity and hearing acuity in the 2000hz range did not predict overall *d'*, and did not predict performance specifically for the 2006hz *d'*. Both correlational and regression analysis revealed this non-significant relationship. Auditory hearing levels was expected to be positively correlated with *d'* score related to behavioral

sensitivity to deviants. Although it seemed reasonable that the better one's hearing is, the better one performs on a task which relies on the ability to discriminate between sounds. However, this effect was not found, for both overall *d'* score but also for the smallest deviant *d'* score. Although research on clinical groups have found that clinical impaired level of hearing is associated with decreased *d'* (Oates et al., 2002), the current study involved normal hearing subjects, and the inverse of hearing loss, hearing acuity may not impact the ability to discriminate between deviants when hearing is within a normal range.

Behavioral performance is different from more apparent automatic nature to prediction error (Näätänen et al., 2007), in that it requires both the recognition and response of the participant, and can therefore be argued to be more susceptible and vulnerable to variables such as attention, cognition and reaction time. The relationship between hearing and perception of sound may be a complex process, where small deficits in sensory functioning in some individuals may be compensated for, resulting in a larger difference in behavioral performance (Ross et al., 2007). Although the former argument was made in the context of hearing differences in age, it still applies to a general notion of the complexity of the relationship between the ability to hear and performance related to perceptual mechanisms of hearing. Compensatory mechanisms have been found in response to hearing loss (Campbell & Sharma, 2013; Irvine & Rajan, 1996), which may indicate a propensity to compensate for differed hearing during behavioral performance through other cognitive mechanisms. Although one could make the argument that the two tasks in the present study are analogues, in that both require a push of button in response to a stimulus change, this would be comparable in terms of the cognitive and auditory mechanisms which they may prompt, the non-significant relationship still remains enigmatic. Differences in young and old with normal hearing have been found for event-related potentials, such as N1 and P1, where hearing loss in older age was related to increased N1 latencies. These findings elucidate some of the otherwise complex relationships that may underlie hearing and perception of sound (Tremblay et al., 2003), which illustrates that the assumption of hearing acuity in the normal hearing range and subsequent performance on behavioral discrimination tasks may have been unwarranted.

Bernarding et al.,(2013) found that with lower levels of hearing acuity is linked to higher cognitive demands in listening discrimination tasks, which could help explain why scores on auditory performance doesn't necessarily predict scores on behavioral oddball paradigm. It may be the case that any differences in hearing is made up by increased cognitive

effort, which compensates for hearing levels, therefore obscuring the relationship between hearing acuity and behavioral oddball performance. It may also be the case that the behavioral task was not particularly difficult, as oppose to the auditory test which explores the very thresholds of the auditory perception in the participants, so the cognitive demands put on the participants with perhaps lower levels of hearing was not high enough for the behavioral task. Bernarding and colleagues (2013) has noted that young participants with normal hearing, 21-35 years of age, did not differ in their *d'* score between an easy and difficult auditory discrimination task, but middle aged normal hearing individuals (age 40-60) differed in *d'* scores for easy and difficult auditory discrimination tasks, which may indicate an increase cognitive load as a better indicator of behavioral discrimination performance rather than auditory scores themselves. The *d'* scores for the normal hearing individuals was compared to those with mild impaired hearing, which was found to be equal. If one would expect hearing acuity to be correlated with behavioral performance, there would be a difference in these scores between those with normal hearing and those with hearing impairments. This is not found, again pointing to the potential cognitive mechanisms compensating for hearing difficulty.

Another explanation for the non-significant findings may be related to the statistical analysis used and the small sample size. For regression analysis it is recommended to use between 15-40 participants for each explanatory variable in a Regression analysis (Dancey & Reidy, 2007).

Considering that results indicated that auditory discrimination for the behavioral oddball paradigm worked as intended, where there were significant differences in scores between deviant types. Perhaps the four increments of change were not sensitive enough to those within a normal hearing range, and that more increments may have better profiled the ability to discriminate between stimuli, leading to hearing acuity better predicting *d'* scores. This is however speculative.

Implications

The implication of the current study involves both the basic research and clinical domains. Firstly, although a failure to detect any change in glutamate in response to rapid auditory stimulation, the interaction effects may yield some promise for the use of the fMRS under the current experimental protocols. For basic research this may help elucidate the debate regarding pre- and perceptual processes and how these related to the neural dynamics of excitatory and inhibitory circuitry. Specifically, it may be instrumental in alleviating some

of the debate between sensory memory and adaptation account of the phenomenon. By potentially revealing the suppression and lateral inhibitory mechanisms by measuring glutamate and GABA dynamics, it may help strengthen the account of both the adaptation (May & Tiitinen, 2010) and the predictive processing account (Garrido et al., 2009). It may help further help explore the role of glutamate and GABA activity in Gamma band and ERP's recorded during stimulus presentation and deviation, and how these frequency bands and ERP's related to prediction error elicitation (Askew & Metherate, 2016; Friston, 2005). Moreover, it may be especially valuable in uncovering the physiological dynamics purported to underlie the predictive processing hierarchy, whereby purposed top down and lateral modulation through inhibitory GABA activity suppress and regulate excitatory prediction error potentials mediated through glutamate functioning (Friston et al., 2016; Garrido et al., 2009). And how this excitatory signal drives changes in top down predictions at different time scales as it propagates through the layers of the cortex, from lower areas generating prediction error in short time scales to the higher areas generating prediction error overs longer time scales (Parr et al., 2018).

This may also have implication for understanding pathologies such as Schizophrenia and Dyslexia. For Schizophrenia it may help elucidate the propositions that faulty NMDA receptors which lead to glutamate hypofunction and failure to regulate inhibitory function in E/I circuitry which contributes symptoms such as cognitive impairments (Lewis & Moghaddam, 2006). Moreover, it may help test some of the physiological propositions of NMDA mediated activity in the Dysconnection hypothesis, whereby a failure to properly suppress and regulate prediction errors is proposed to be at the core of the disease (Friston et al., 2016). It may also help explore the neurobiological propositions made by the neural noise hypothesis of Dyslexia, where imbalances in the E/I circuitry of the auditory cortex lead to failure to properly synchronize neural activity and decreasing discrimination ability, and the eventually gives rise to symptoms such a reduced phonological awareness and reading ability (Hancock et al., 2017).

Future consideration

Something that became apparent during partitioning and binning the spectral data was the potential influence of multiple stimuli in the later bins (400ms, 500ms, 600ms and 700ms) for the analysis. Since SOA, the time of stimulus onset until the next stimulus onset, was 370ms, one stimulus extra would always partially or fully be included in these bins. One solution to this could be to find the average Glx measurement for the extra stimulus and

subtract that from the bin. For instance, in a deviant bin at 700ms which would contain one deviant stimulus and one standard stimulus, the average measure for standard stimulus bins would be calculated, and this score would then be subtracted from the bin. This would potentially yield a closer proximate of what the true deviant stimulus Glx would be at this time point. This method would of course rest on a gross simplification of how the glutamate response evolves over time.

Using different techniques which help differentiate glutamine and glutamate may be warranted in order to make inferences about excitation and neural activity in general. Glutamine is the primary supply for the synthesis of glutamate and GABA in the brain (Petroff, 2007). The synthesis of glutamine to glutamate is proportional during neurotransmission (Petroff, 2007), meaning that the temporary changes in the ratio of glutamine and glutamate can be a valuable marker of neurotransmission (Öngür et al., 2011). An increase in glutamine with the reciprocal decrease in glutamate can be indicative of a neurotransmission process, where glutamate is released then transported and converted to glutamine in the glial cells. This has been measured during stimulation of animals in high field strength MRS procedures (Petroff, 2007). Due to the rapid nature of glial glutamate transporters moving the glutamate from the extracellular environment into the glial cells where it is then converted to glutamine, it may be a much better index of neurotransmission than just an increase in Glx alone. Several $_1$H-fMRS techniques have been proposed for the separation of glutamate and glutamine (Hu et al., 2007; Mullins et al., 2008; Wijtenburg & Knight-Scott, 2011) and recently GABA edited MEGA-PRESS sequences have been used to separate glutamate and glutamine, but as the researchers noted, was optimal only for certain areas of the brain (Sanaei Nezhad et al., 2020).

Conclusion

In conclusion, the present study found that detecting increases in glutamate in response to auditory stimulation in general may or may not be feasible, but increases to deviation stimulation among a train standard tones may be feasible when acquisitions are made within the time frame of 300ms to 400ms. The present study also shows that it is possible to measure Glx and GABA with the use of oddball experiments. The study serves as a proof of principle of the technique used here. The study also finds that glutamate increases to deviating stimuli, but that the visible glutamate increase does not temporally coincide with EEG indices of prediction error.

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Appendix A

Edinburgh Handedness Inventory

Please indicate your preferences in the use of hands in the following activities *by putting + in the appropriate column.* Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, *put ++.* If in any case you are really indifferent *put + in both columns.*

Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

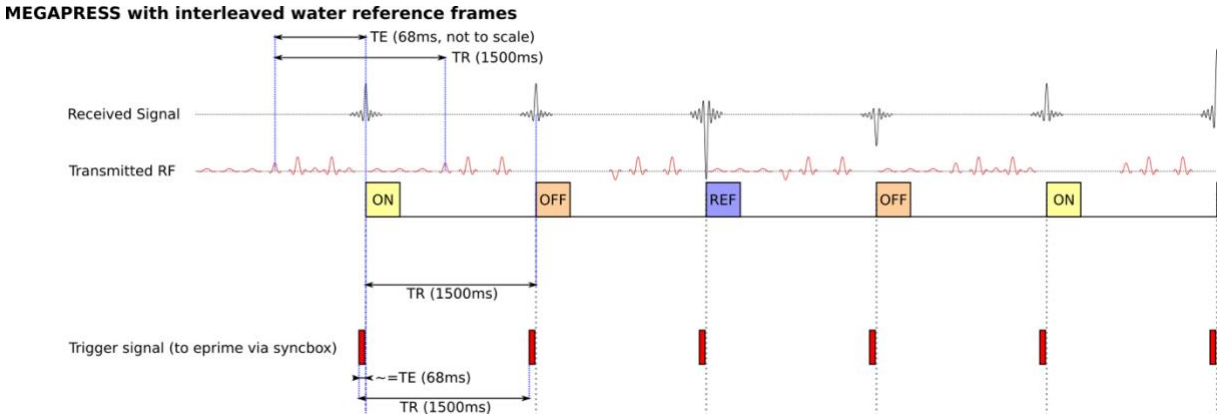
Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

		LEFT	RIGHT
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (without fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking Match (match)		
10	Opening box (lid)		
i	Which foot do you prefer to kick with?		
ii	Which eye do you use when using only one?		

L.Q.		Leave these spaces blank	DECILE	

Appendix B

MEGA-PRESS acquisition sequencing



Appendix B. Figure illustrating the timing and sequencing parameters for the fMRS acquisition (A. R. Craven, personal communication, May 28th, 2020)