Levels of γ-Aminobutyric acid in the ventral lateral prefrontal cortex as a predictor of underdetermined selection ability

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Abstract

The inhibitory neurotransmitter γ-Aminobutyric acid (GABA) and the excitatory neurotransmitter glutamate are the most abundant neurotransmitters in the brain. Together these neurotransmitter systems have been implicated in brain regions related to executive function, specifically, in the ventral lateral prefrontal cortex (VLPFC) and the dorsal lateral prefrontal cortex (DLPFC). One measure of executive function that these systems influence, is the process of obtaining a winning option amongst competing alternatives, known as selection. Selection can be split into two categories; underdetermined selection and prepotent selection. Underdetermined selection refers to selection amongst many task related options while prepotent selection refers to the ability to select relevant information in the face of a dominant option that is task irrelevant. Moreover, previous studies have shown a relationship between selection and traits related to psychopathology, such as anxiety and depression. The current study seeks to examine the pathways linking GABA to regional brain activation in the prefrontal cortex to performance on selection based cognitive tasks and to traits related to psychopathology. Using MR spectroscopy, GABA levels were measured in the VLPFC and fMRI was used to measure brain activation during a selection based, verb generation task. Levels of anxiety and depression were measured through the Penn State Worry Questionnaire (PSWQ) and the Mood and Anxiety Symptoms Questionnaire (MASQ). The results show a significant negative correlation between VLPFC GABA concentration and performance on underdetermined selection tasks suggesting that levels of neurotransmitter in the prefrontal cortex can influence the degree to which an individual exerts executive control.

Keywords: GABA, VLPFC, underdetermined selection, anxiety, spectroscopy

Introduction

The goal of this thesis is to examine hypothesized pathways that link neurotransmitters to regional brain activation to cognitive abilities to psychological processes related to psychopathology. As such, it is a multi-level examination focusing of the GABAergic and glutamatergic systems in the prefrontal cortex and their relationship to selection ability in the verb generation task and in turn, to anxiety and depression.

The brain is an electrical network that uses chemical messenger to pass information from neuron to neuron. The most abundant of these messengers are γ-Aminobutyric acid (GABA) and glutamate. GABA is the main inhibitory neurotransmitter in the brain while glutamate is the main excitatory neurotransmitter. These two neurotransmitters will be the focus of the current investigation. In addition, we will focus on the relative levels of these neurotransmitters in lateral prefrontal cortex. Here we do so via magnetic resonance (MR) spectroscopy, which is a form of magnetic resonance imaging (MRI). MRI is a method of neuroimaging that uses a magnetic field to align the protons in the object being imaged. Images are obtained from these protons being knocked out of alignment and measuring of the frequencies that are emitted when the protons return to the proper alignment. MR spectroscopy is a form of MRI that is used to measure levels of specific molecules in a specific region. The region is determined through the placement of a voxel which is a cube from which the measurement will be taken. Voxels can be moved and the dimensions adjusted according to the region of interest.

While GABA and glutamate are found throughout the brain, here we focus on their concentration in the prefrontal cortex. The prefrontal cortex has been shown to be an important

brain region for executive function (Banich, 2009). Executive function is an umbrella term for a collection of processes which predominantly consists of goal oriented behavior such as goal formation, planning, and execution (Jurado & Rosselli, 2007). Duncan and Owen (2000) demonstrated this regional differentiation through the use of functional magnetic resonance imaging (fMRI) while participants completed tasks associated with executive function. The tasks manipulated various cognitive demands that include response conflict, task novelty, perceptual difficulty, and working memory delay and number of elements. Functional imaging during each task showed that the pattern of activation for all five of the cognitive demands tested is distributed along the lateral regions of the prefrontal cortex for both hemispheres.

Previous research has suggested that dorsal vs. ventral regions of prefrontal cortex are involved in distinct types of executive processes. One such executive process is that of selection. To achieve a goal in executive function there must be an option that wins amongst the competing alternatives, such as possible responses to a stimulus. The process of obtaining a winning option is referred to as selection. Selection can be broken into two types; prepotent and underdetermined. Prepotent competition refers to selection in which there is a strong association to a response type that must be overcome to reach the correct decision. One example would be responding to the noun “fork” with a verb, when the word “fork” is more strongly associated with other nouns such as “knife” . Underdetermined competition occurs when selection involves choosing amongst multiple suitable options. An example of this would be “ball” which has many associated verbs such as throw, kick, hit, toss, etc. Snyder, Banich, and Munakata (2014) used fMRI to assess brain activation during a verb generation task in which the trials were crossed between high and low prepotent conditions and high and low underdetermined conditions. The results showed that there was greater activation in the dorsal regions of the prefrontal cortex

during high vs. low prepotent conditions and greater activation in the ventral regions during the high vs. low underdetermined conditions.

Of interest is that at least some research suggests that not only are these dorsal vs. ventral regions involved in different types of executive function, but that they also may be related to individual differences in characteristics related to psychopathology. Decreased DLPFC activity has been observed in individuals who report higher levels of anhedonic depression (Herrington, Heller, Mohanty, Engels, Banich, Webb, & Miller, 2010) and decreased VLPFC activity has been observed in individuals with higher levels of anxious apprehension, which can be thought of as worry (Snyder, Hutchison, Nyhus, Curran, Banich, O'Reilley, & Munakata , 2010) (See Figure 1).

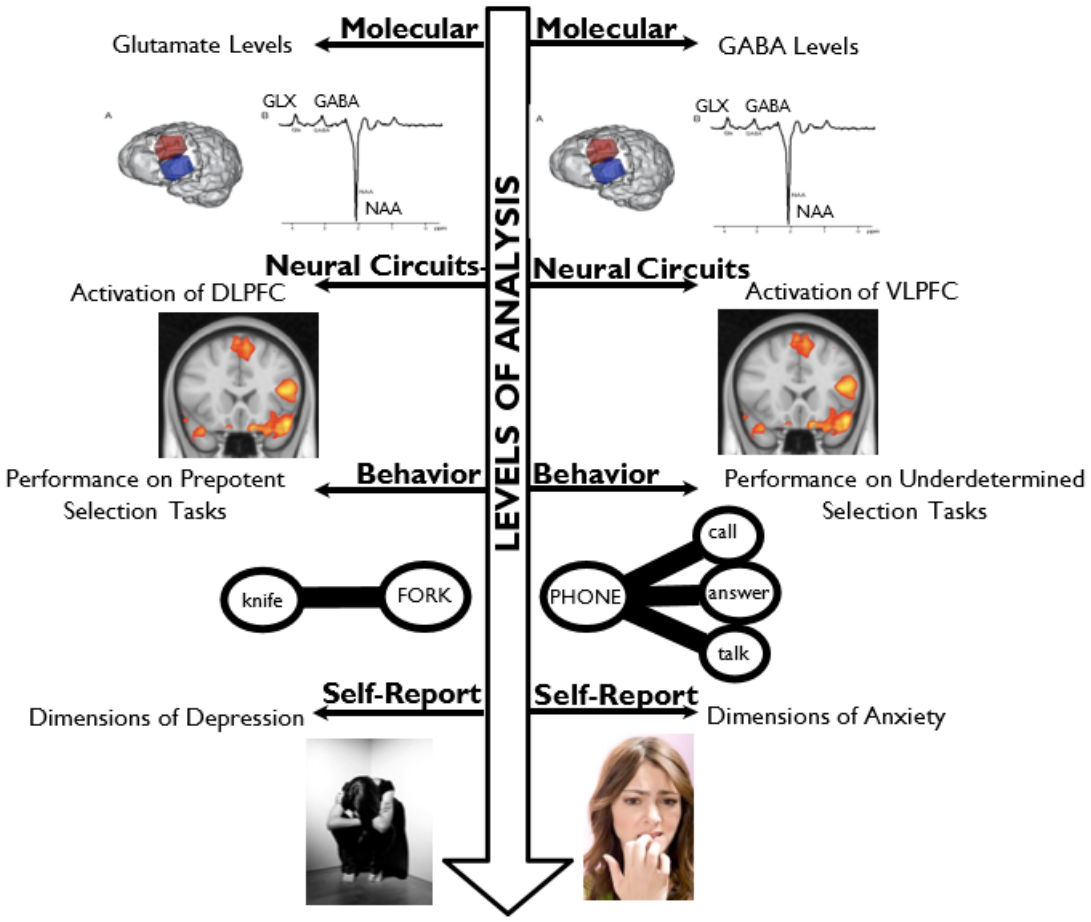

Figure 1 Proposed GABA and Glutamate pathways and related brain region, behavior, and psychopathology

Studies utilizing fMRI and MR spectroscopy have implicated that the neurotransmitter GABA also plays a critical role in undetermined selection, that is the process of selecting among multiple competing options (Snyder et al., 2010; de la Vega, Brown, Snyder, Singel, Munakata, & Banich, 2014). It is theorized that GABA affects selection through lateral inhibition. Lateral inhibition is the process through which, when activated, GABAergic neurons release GABA onto the surrounding neurons. This release of GABA inhibits the neighboring neurons which are also

receiving GABA from multiple other neurons. Due to multiple neurons releasing GABA some neurons become more inhibited than others and eventually a single neuron configuration remains activated (Miller & Cohen, 2001). The theory for selection is that each possible option corresponds to a neuron configuration and the remaining configuration after lateral inhibition is the winning option.

Snyder et al. (2010) used fMRI to measure regional brain activation in the VLPFC of participant as they complete the verb generation task. In the verb generation task participants are presented with a noun and must verbally respond with the first verb that they think of. The data showed that participants with lower levels of VLPFC activation took longer to produce a response during the task. A secondary study by Snyder et al. (2010) demonstrated improvement on the verb generation task when participants were given the GABA agonist midazolam. Together these results suggest a relationship between VLPFC activation, GABA, and selection. However, this study did not measure levels of GABA in these brain regions.

De la Vega et al. (2014) used MR spectroscopy to investigate whether individuals with lower levels of GABA in the lateral PFC had decreased underdetermined selection ability. By using spectroscopy, they were able to directly test the relationship between GABA levels and the VLPFC that was implicated in the midazolam study of Snyder et al (2010). They found that selection may not be linked just to GABA levels, but the ratio of GABA (inhibitory function) to glutamate/glutamine (GLX) (excitatory function). De la Vega et al. (2014) has shown that a higher ratio between GABA and GLX predicts increased ability in the high vs. low undetermined selection condition. The finding that the balance between GABA and GLX, and thus the balance between inhibition and excitation, is predictive of undetermined selection ability may indicate that the relative balance of neurotransmitter systems is important. This ratio has been shown to

be specific in predicting undetermined selection, but did not predict other executive function constructs (de la Vega et al., 2014).

GABAergic function has also been linked to anxiety, which is common disorder (Snyder et al., 2010). Snyder et al. (2010) found that participants that had greater levels of anxiety showed decreased activation of the VLPFC for high vs. low underdetermined selection. The subsequent study with midazolam administration showed improved selection ability. Combining these studies yields a theory that GABA plays a role in the anxiety trait of anxious apprehension, which can be conceptualized as worry, through impaired selection ability. Previous studies have also shown that high levels of anxiety have been linked to low levels of GABA (Lydiard, 2003).The current study is seeking to further understand the relationship between GABA concentration and activation of the VLPFC, underdetermined selection, and anxious apprehension and to formally test the role of GABA in anxious apprehension. The focus will be on levels of GABA in the VLPFC, as measured by MR spectroscopy. The glutamate pathway will be used as a control to test if there is specificity in regard to neurotransmitter function. DLPFC will be used as a control to see if the effects are specific to a given brain region, and prepotent selection will be used as a control to see if the effects are specific to undetermined selection. It is hypothesized that greater increases in reaction time (RT) during high vs. low underdetermined selection conditions in the verb generation task will be negatively associated with GABA levels in VLPFC. Also, VLPFC GABA levels will be negatively associated with both levels of anxiety and activation of the VLPFC during the verb generation task.

While prior studies have examined these issues in emerging adults (i.e., early 20s), in the current study we will examine adolescents. The GABAergic system in the prefrontal cortex is still developing in adolescence (Caballero & Tseng, 2016). Adolescence is also a critical time in

the development of many psychiatric disorders (Paus, Keshavan & Geidd, 2008), which is why we focus on this developmental time period in the current study.

Methods

Participants consisted of 44 adolescent females (17.2 ± 2.0 years old) and 32 adolescent males (17.6 ± 1.7 years old), recruited based on past participation with the GEM Lab at the University of Denver. The GEM (Genes, Environment, and Mood) study is a community based study focusing on genetics, psychological status, and emotional processing in relation to the development of depression and anxiety. All participants spoke English as their first language and did not have any problems with reading. Participants completed two visits to the University of Colorado Boulder. The first visit consisted of computerized behavioral tasks and a clinical interview as well as paper surveys. Then during the second visit participants underwent MRI scanning that lasted approximately 2 hours and 15 minutes. Informed consent was obtained from all participants over the age of 18 and adolescent assent as well as parent permission were obtained for participants under 18. All participants were treated in accordance to the policies of the University of Colorado Institution Review Board.

Neuroimaging

Data Acquisition

A SIEMENS MAGNETOM Trio (3-Tesla) MRI system with a 32-channel head coil was used for structural, functional, and MR spectroscopy data acquisition. To reduce head motion during MRI data acquisition, foam padding was placed around participants' heads. All structural images used for functional volume and alignment and MR spectroscopy voxel placement were T1-weighted MPRAGE images, with a repetition-time [TR] = 2,300 ms, echo time [TE] = 2.07 ms, and flip angle = 8 degrees, with .8 mm x .8 mm x .8 mm voxel. fMRI images collected in conjunction with the verb generation task had a TR = 460 ms, TE = 27.20 ms, and flip angle = 44 degrees, with each image consisting of 56 contiguous slices (thickness = 3 mm) with a multiband acceleration factor of 8. A total of 1400 TRs were acquired over the course of the verb generation task.

Spectroscopy

Two MR spectroscopy voxels were placed following of visible inspection of an individual subject's T1 structural image. The DLPFC voxel was positioned in the middle frontal gyrus (MFG), anterior to the precentral gyrus and posterior to the frontopolar cortex The VLPFC voxel was position in the inferior frontal gyrus anterior to the precentral gyrus and posterior to frontopolar cortex. Mean voxel size across participants was 15.79 (2.00) cm^3 and 16.19 (2.48) cm^3 for the DLPFC and VLPFC voxels, respectively. The voxels were used to determine levels of GABA and GLX in both brain regions as well as water. GLX levels were measured using the PRESS sequence and GABA was measured using the MEGA-PRESS sequence as outlined in de la Vega et al (2014). From each voxel the concentration of GABA or GLX was obtained by measuring the levels of GABA and GLX against the baseline of water and dividing by the volume of the respective voxel.

Functional Brain Activation

Measures of brain activation were determined by the BOLD Method for participants while they performed the verb generation task (see below). For purposes of this thesis, percentage signal change in the BOLD signal were obtained for two regions of interests, one in the DLPFC and one in the VLPFC, while individuals were performing the verb generation task (see below). These regions of interest were selected from the peak activation reported by Snyder et al. (2014) (MNI coordinates: DLPFC -48,18,36; VLPFC -42,32, -8). A 5-voxel sphere around these peak locations and the average percentage signal change within that sphere was calculated. Activation for each sphere was calculated for two contrasts of interest. One contrast was activation for prepotent selection, which was calculated as the percent signal change of the high prepotent/low underdetermined condition vs. the low prepotent/low underdetermined condition. The other contrast was for underdetermined selection activation, which was the percent signal change of high underdetermined/low prepotent condition vs. the low underdetermined/low prepotent condition.

Verb Generation

A verb generation task was completed in the MRI scanner following the same procedure outlined in Snyder et al. (2014). Participants were presented with a noun and were tasked with providing the first verb that came to mind (e.g., "eat" for "spoon"). The noun was presented for 3,000 ms with 1,000 ms for the inter-trial interval. The task contained 100 nouns over 10 blocks of 10 trials. The design for the nouns was 2 x 2 with high and low prepotent competition crossed with high and low underdetermined competition. High prepotent conditions used nouns that are

strongly associated with non-verbs (e.g., other nouns, such as fork and knife) and low prepotent conditions were strongly associated with verbs (e.g., scissors and cut) . High underdetermined competition conditions presented nouns that were associated with multiple verbs (e.g., ball and throw, kick, hit, toss, etc.), and low underdetermined conditions were associated with just a few verbs (e.g., gift and give, receive). Examples of prepotent and underdetermined stimuli for each condition are also shown in Figure 2. The task lasted for approximately 9 minutes. Responses were recorded in the scanner using a fiber optic microphone. Responses that did not contain a verb or were unintelligible were removed from analysis. Reaction times from voice onset were obtained through using the linguistic software PRAAT. Onset outputs from PRAAT were inspected and corrected by hand when necessary. The reaction time between the presentation of the noun and the onset of the response was measured for each trial.

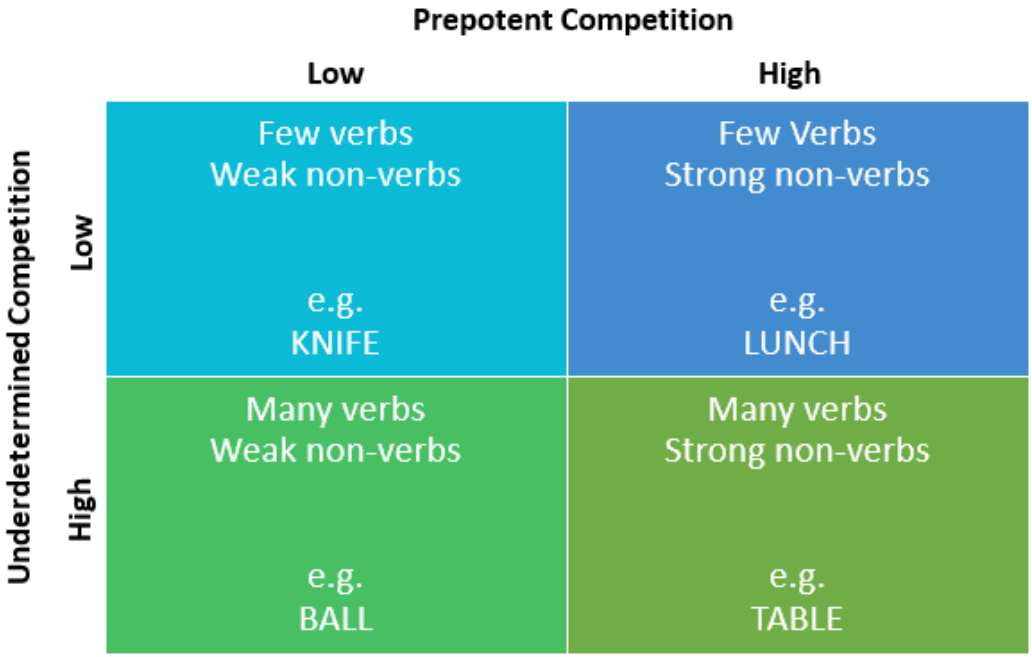

Figure 2 Trials design of the verb generation task as outlined in Snyder, Banich, and Munakata (2014)

The reaction times were divided into two categories; underdetermined and prepotent selection. The measure of undetermined selection was calculated as [(high underdetermined/low prepotent)- (low underdetermined/low prepotent)]/ (low prepotent/low underdetermined). Hence, higher scores represent more difficulty in selecting amongst alternatives when there are many options (i.e., undetermined selection). Prepotent reaction times were calculated as of [(high prepotent/low underdetermined)- (low prepotent/low underdetermined)]/ (low prepotent/low underdetermined). Low prepotent and low underdetermined trials were used as a baseline to determine the percentage increase of reaction time as a result of high demand conditions.

Psychopathology Questionnaires

Prior to the MRI session, participants completed a behavioral session in which they completed questionnaires, in addition to a neurocognitive battery and semi-structured clinical interview. Measures of individual differences in anxiety and depression dimensions were obtained from these questionnaires. Anxious apprehension (AAp) was calculated from the sum of all items in the Penn State Worry Questionnaire (PSWQ) (Meyer, Miller, Metzger, & Borkovec, 1990). AAp is being used as a measure for the cognitive aspect of anxiety. As a contrast, we also measured Anhedonia (Anh), which was calculated from the 90-item Mood and Anxiety Symptom Questionnaire (MASQ), with anhedonic depression (Anh) consisting of the sum of items on the ANH subscales (Watson, Weber, Assenheimer, Clark, Strauss, & McCormick, 1995). ANH is being used to measure levels of anhedonic depression of participants which is a cognitive aspect of depression. In addition to examining each construct separately, a difference score between the

Z scores for AAp and Anh (AAp-Anh) will also be used since there is often high levels of comorbidity between anxiety and depression. This score will show if a participant is more anxiety pure, signified by a positive score, or more depression pure, signified by a negative score.

Results

A. Do individual differences in neurotransmitter level predict regional brain activation during a cognitive control task?

   Due to the lack of prior research on this topic no predictions were made regarding the relationship between neurotransmitter level and region brain activation. Neither the correlation between an individual's VLPFC GABA concentration and brain activation in VLPFC for the contrast of high vs. low underdetermined selection ($r= -0.0985$, $p=0.4205$), nor between an individual's concentration of GLX in the DLPFC and brain activation in DLPFC during high vs low prepotent selection ($r= -0.116$, $p=0.3418$) were significant.

B. Do individual differences in neurotransmitter level predict the behavioral ability to exert cognitive control?

As predicted, a significant correlation was found between VLPFC GABA concentration and percent increase in RT for high vs. low underdetermined selection from the verb generation task ($r= -0.230$, $p<0.05$) (Figure 3), such that those individuals with lower concentrations of VLPFC GABA exhibited elongated reaction times when there were many potential words that could be generated to a verb (high undetermined selection) as compared to when there were few words that could be generated (low undetermined selection)

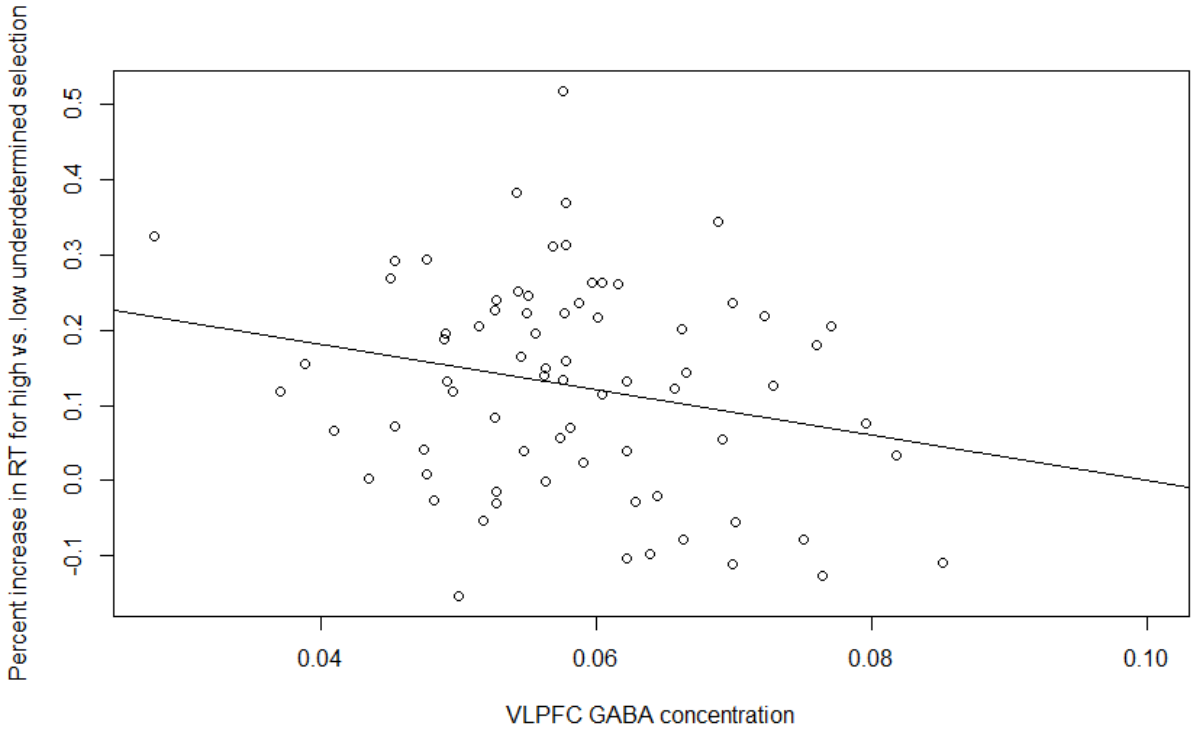

Figure 3 Correlation between GABA concentration in the VLPFC and percentage increase in RT for high vs. low underdetermined selection in the verb generation task

Additional tests were then performed to determine the specificity of this result. To test whether the results were specific to GABA as compared to the other main neurotransmitter under investigation, GLX, we examined the correlation between GLX concentration in VLFPC and percentage increase in RT for high vs. low underdetermined selection. This correlation was not significant (r= -0.142, p=0.228) (See Figure 4).

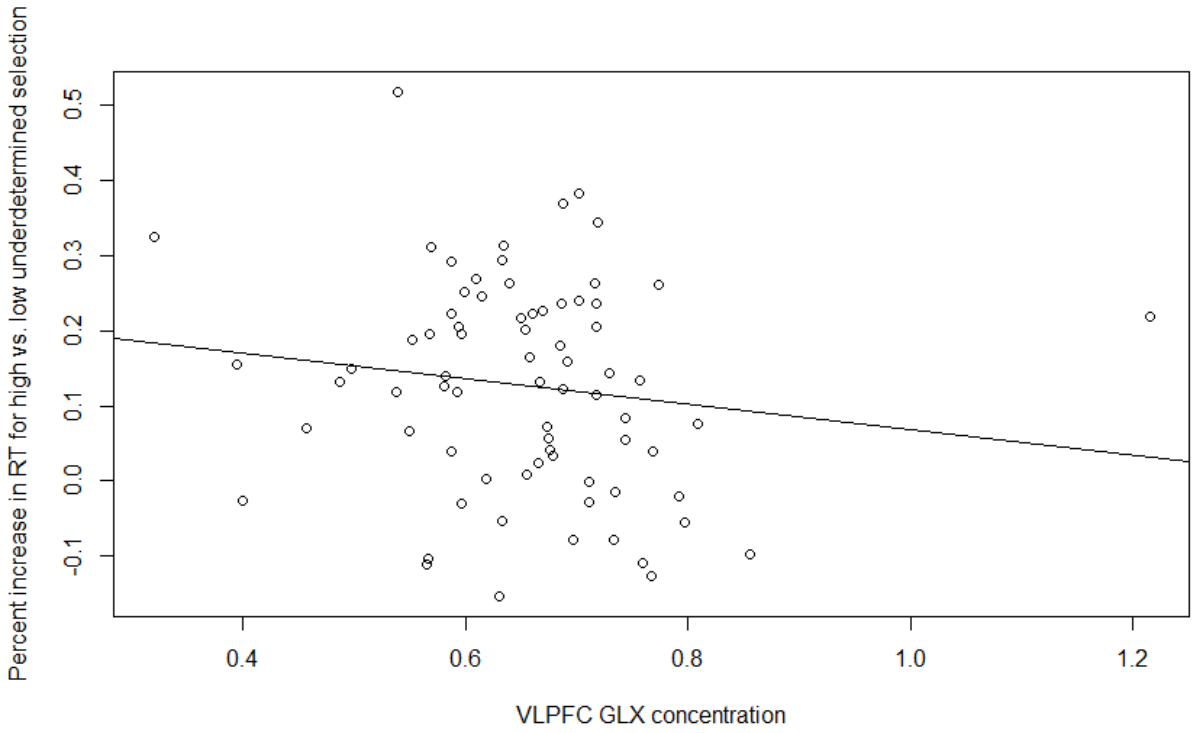

Figure 4 Correlation between VLPFC GLX concentration and percentage increase in RT for high vs. low underdetermined selection in the verb generation task.

To test the specificity of the brain region, the relationship between DLPFC GABA concentration and percentage increase in RT for high vs. low underdetermined selection was calculated (Figure 5). This relationship yielded a non-significant correlation of r= -0.129, p=0.273.

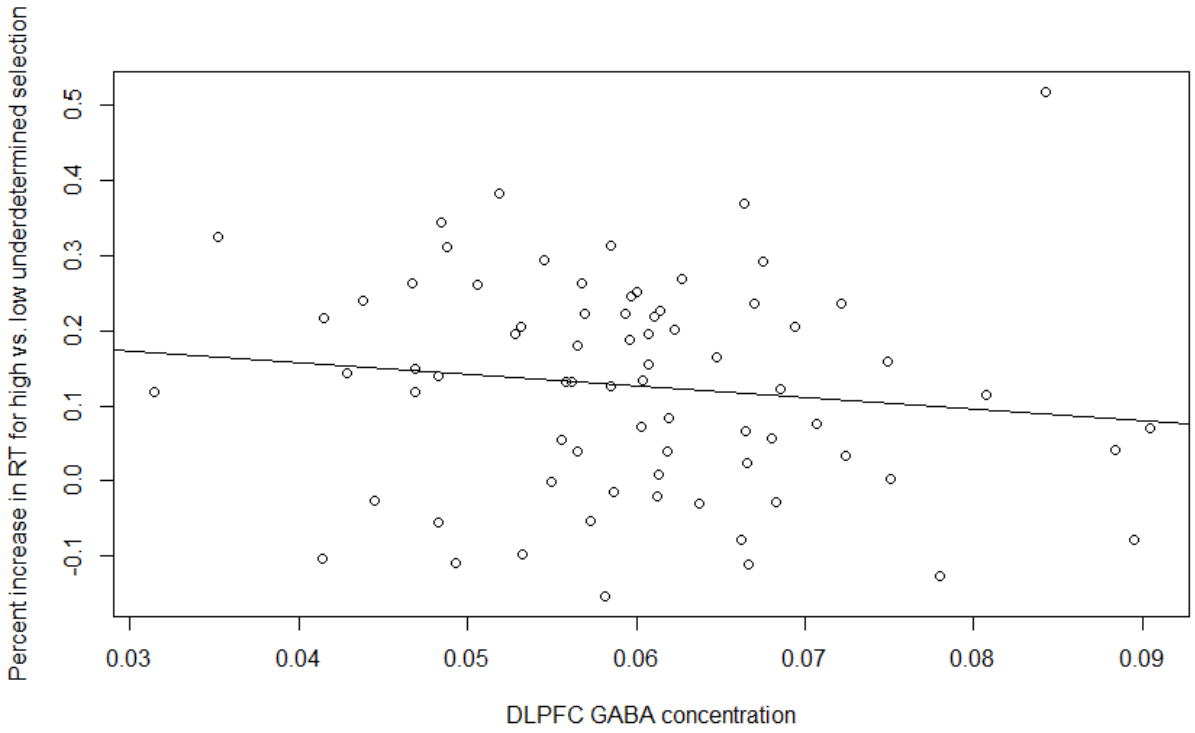

Figure 5 Correlation between GABA concentration in the DLPFC and percentage increase in RT for high vs. low underdetermined selection in the verb generation task.

To test the specificity with regards to psychological constructs, we examined the correlation between VLPFC GABA concentration and percentage increase in RT for high vs. low prepotent selection. This correlation was not significant (r= 0.0845, p=0.474) (see Figure 6).

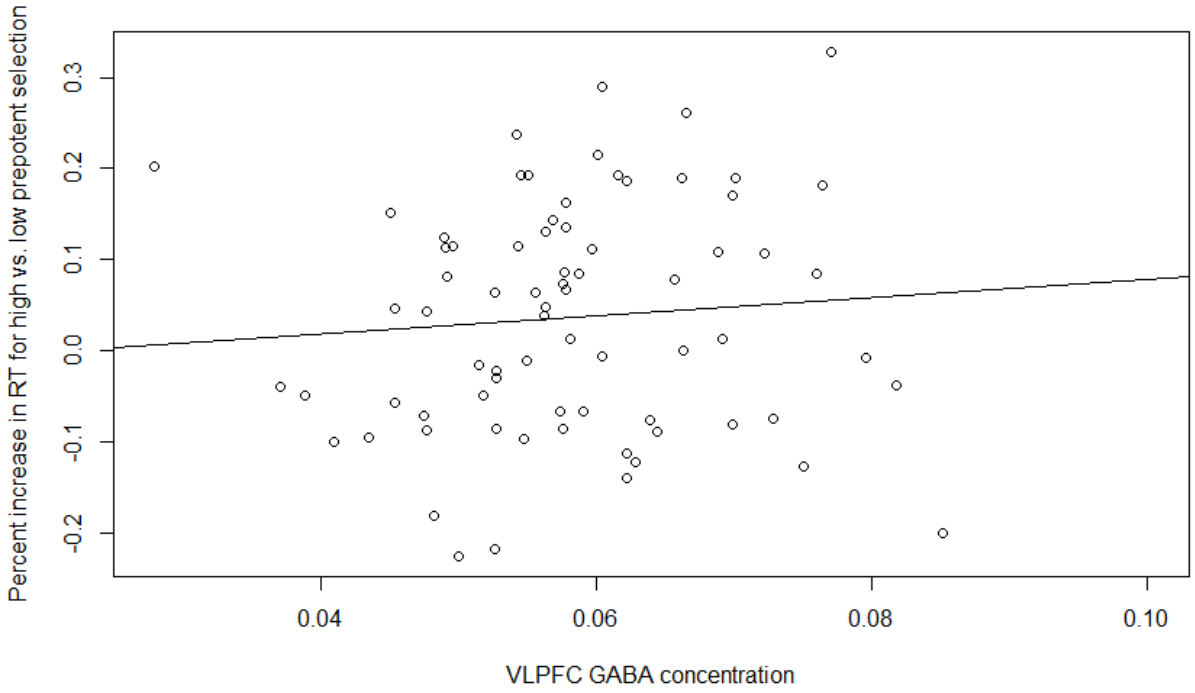

Figure 6 Correlation between VLPFC GABA concentration and percentage increase in RT for high vs. low prepotent selection in the verb generation task.

A Steiger's Z test of correlated correlations was performed on all correlations testing the specificity of the relationship found between VLPFC GABA concentration and percentage increase in RT for high vs. low underdetermined selection. The only test to yield a significant Z value was that of the correlations between VLPFC GABA concentration and percentage increase in RT for high vs. low underdetermined selection as compared to VLPFC GABA concentration and percentage increased RT for high vs. low prepotent selection ($Z= -2.9257$, $p<0.01$). Thus, indicating a high degree of specificity with regards to the psychological processes influenced by VLPFC GABA concentrations.

C. Do neurotransmitter levels predict symptoms anxious apprehension (worry)?

There was no significant correlation between VLPFC GABA concentration and AAp ($r= 0.187$, $p= 0.875$) nor between VLPFC GABA concentration and AAp-Anhedonia ($r= -0.0395$, $p=0.7346$).

Discussion

The neurotransmitters GABA and glutamate are critical to brain functioning and may play a role in psychological disorders such as anxiety and depression. The results of this study show that there was no significant relationship between concentration of GABA in the VLPFC and activation of the VLPFC during the verb generation task. This lack of relationship could potentially be due to morphological differences in adolescents. The prefrontal cortex is the last region of the brain to develop and thus would not be fully formed in the adolescents being studied.

Another possibility for the lack of a relationship could be a discrepancy between the specific region of activation that was measured and the location of the spectroscopy voxel. The regions in which activity was measured were those of the peak activation during underdetermined selection in a previous study (Snyder et al., 2014). However, Snyder et al. (2010) used an older population than the current study which could result in differing areas of peak activation. The placement of the spectroscopy voxels also varies from person to person depending on their specific neuroanatomy. As a result, the voxels may not have overlapped completely with the activation region of interest (ROI). This would lead to a small part of the

voxel obtaining GABA concentrations from within the ROI, and the rest of the voxel obtaining GABA concentrations outside of the ROI and becoming noise.

While concentrations of GABA in the VLPFC were not predictive of regional activation, they were predictive of performance on underdetermined selection in the verb generation task. As predicted, there was a statistically significant negative correlation between VLPFC concentration of GABA and percentage increase RT for the high vs. low underdetermined selection conditions. This indicates that those individuals that have lower levels of GABA in the VLPFC take longer to choose a verb during the task under conditions of multiple as compared to few verb options. The data suggested some specificity to these findings. Additional analyses yielded non-significant correlations between VLPFC GLX concentrations and percentage increase in RT for high vs. low underdetermined selection suggesting specificity of the neurotransmitter. There was also no significant relationship between DLPFC GABA concentration and percentage increase in RT for high vs. low underdetermined selection nor between VLPFC GABA concentration and percentage increase in RT for high vs. low prepotent selection demonstrating regional brain and behavioral specificity respectively.

The results also showed that there was not a significant relationship between VLPFC GABA concentration and anxious apprehension. Adolescence is the time period in which psychopathologies begin to develop and emerge. It is possible that the traits of anxiety and depression are still emerging in this sample and thus did not show a relationship with the levels of GABA. Conversely, the lack of a relationship may be due to the GABAergic system in the brain still developing.

These results are consistent with the neural mechanism proposed by Snyder et al. (2010). Snyder et al. (2010) found that performance on underdetermined selection was impaired in

participants with anxiety and improved upon the administration of the GABA agonist midazolam. Hence, it was concluded that GABA plays a role in selection and anxiety. However, since midazolam acts on the whole brain there was no evidence that GABA levels specifically in the VLPFC were causing the effect. Snyder et al. (2010) and Snyder et al. (2014) found a relationship between activation of the VLPFC and underdetermined selection performance, providing a region of interest for this study. Through the use of MR spectroscopy this study was able to provide a direct link between GABA concentration in the VLPFC and underdetermined selection performance.

This study however, did not replicate the relationship between GABA and underdetermined selection found by de la Vega et al. (2014). In that study, it was shown that the ratio between GABA and GLX was predictive of performance for underdetermined selection and that higher levels of GABA were related to better performance. A supplementary analysis between the ratio of GABA/GLX and percentage increase in RT for high vs. low underdetermined selection was conducted in the current study to try and replicate the de la Vega et al. (2014) findings and no significant correlation was found. The discrepancy between these findings may be due to the ages of the participants. De la Vega et al. (2014) assessed this relationship in a population with mean age of 21 while the current study had a mean age of roughly 17 years old. By assessing a population further along in development, de la Vega et al. may have found a relationship because the GABAergic and glutamatergic systems, as well as the prefrontal cortex, are nearly done developing.

While this study provides evidence for the role of GABA concentration in the VLPFC for underdetermined selection performance it remains to be seen how this plays a role in psychopathology such as anxiety or how it changes with age. The cohort that was used in this

study is part of a larger longitudinal study in which they will return for testing after 2 years. Following the second time point of testing, these analyses may be run again to see how time and growth affects the results, if at all. Assessing these participants again in two years is important to determine how the relationships of VLPFC GABA concentration and regional activation, underdetermined selection ability, and anxiety change as the brain continues to develop and development begins to stabilize. The participants included in this study are adolescents in a critical period of development. Studying them during this period and at two separate time points will allow us to see how brain development and maturation effects the GABAergic system and its role in selection and anxiety. In addition to the adolescents, data is being collected on a subset of adults that are the parents of participants. This additional data set will serve to further study whether the results found are specific to adolescents or extend across all age ranges.

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