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Alcohol Decreases Baseline Brain Glucose Metabolism more in Heavy Drinkers than Controls but has no effect on Stimulation-Induced Metabolic Increases

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ABSTRACT

During alcohol intoxication the human brain increases metabolism of acetate and decreases metabolism of glucose as energy substrate. Here we hypothesized that chronic heavy drinking facilitates this energy substrate shift both for baseline and stimulation conditions. To test this hypothesis we compared the effects of alcohol intoxication (0.75 g/kg alcohol versus placebo) on brain glucose metabolism during video-stimulation (**VS**) versus when given with no-stimulation (**NS**), in 25 heavy drinkers (HD) and 23 healthy controls each of whom underwent four PET-^{18}FDG scans. We showed that resting whole-brain glucose metabolism (placebo-**NS**) was lower in HD than controls (13%, p=0.04); that alcohol (compared to placebo) decreased metabolism more in HD (20±13%) than controls (9±11%, p=0.005) and in proportion to daily alcohol consumption (r=0.36, p=0.01) but found that alcohol did not reduce the metabolic increases in visual cortex from **VS** in either group. Instead, **VS** reduced alcohol-induced decreases in whole-brain glucose metabolism (10±12%) compared to **NS** in both groups (15±13%, p=0.04), consistent with stimulation-related glucose metabolism enhancement. These findings corroborate our hypothesis that heavy alcohol consumption facilitates use of alternative energy substrates (i.e. acetate) for resting activity during intoxication, which might persist through early sobriety, but indicate that glucose is still favored as energy substrate during brain stimulation. Our findings are consistent with reduced reliance on glucose as the main energy substrate for resting brain metabolism during intoxication (presumably shifting to acetate or other ketones) and a priming of this shift in heavy drinkers, which might make them vulnerable to energy deficits during withdrawal.

INTRODUCTION

Among substances of abuse, alcohol is the one most widely consumed. It is estimated that 56% of Americans 18 years or older consume alcohol at least once a month (SAMHSA, 2012a). Though the majority of individuals use alcohol in moderation, it is estimated that 7.1% are heavy drinkers (5 or more drinks/day on at least 5 different days in the past 30 days) (SAMHSA, 2012b). Thus understanding the effects that heavy alcohol drinking has on the human brain is crucial for developing interventions to minimize potential adverse effects.

Brain imaging studies have shown that acute alcohol administration decreases glucose utilization by the resting human brain, which was originally interpreted to reflect decreases in brain activity (de Wit et al., 1990; Volkow et al., 1990; Wang et al., 2000; Schreckenberger et al., 2004). However, subsequent studies showed that even low doses of alcohol, with minimal behavioral effects, significantly decreased baseline brain glucose metabolism (Volkow et al., 2006). Moreover, alcohol-induced reductions in brain glucose metabolism were larger than those induced by doses of lorazepam that resulted in greater sedation (Volkow et al., 1993). This prompted the hypothesis that during alcohol intoxication the brain increases its metabolism of the alcohol metabolite acetate, while decreasing glucose metabolism. Specifically, acetate, which serves as an energy substrate for astrocytes (Cruz et al., 2005), is readily taken up into the brain, and though its concentration in blood is normally low, it rises significantly during alcohol intoxication (Waniewski and Martin, 1998). Indeed using PET and [^{11}C]acetate, we recently showed that during alcohol intoxication the brain increased the metabolism of acetate and decreased the metabolism of glucose (Volkow et al., 2013). We also reported that heavy drinkers when compared to controls showed an overall trend like elevation in brain acetate metabolism though no difference in alcohol induced increases in acetate metabolism (Volkow et al., 2013). Similarly, a recent magnetic resonance spectroscopy (MRS) study also reported greater acetate metabolism in the occipital cortex for heavy drinkers studied during sobriety than for controls (Jiang et al., 2013), suggesting a shift to acetate metabolism in heavy drinkers that might persist beyond the intoxication state. Here, we test the hypothesis that repeated heavy alcohol use is associated with a decrease

in the brain's reliance on glucose as the main fuel both for baseline (rest) and for sensory stimulation conditions.

For this purpose we used PET and ^{18}FDG to evaluate the effects of alcohol intoxication (0.75 g/kg alcohol compared to placebo) and video-stimulation (**VS;** compared to no-stimulation, **NS**), on brain glucose metabolism in a cohort of 25 heavy drinkers (HD) and 23 healthy normal controls (NML) each of whom underwent four randomized PET-^{18}FDG scans (placebo-**NS**, alcohol-**NS**, placebo-**VS**, alcohol-**VS**). We hypothesized that: 1) alcohol-related decreases in glucose metabolism would be larger for HD than for NML and associated with alcohol consumption history; and that 2) during alcohol intoxication the metabolic increases in visual cortex from **VS** would be similarly attenuated due to a shift to alternative brain energy substrates (presumably acetate or other ketone bodies).

MATERIALS AND METHODS

Subjects: The effects of acute alcohol administration (0.75 g/kg) on brain glucose metabolism were measured in 23 healthy controls (33 ±7 years of age; 12 males, 11 females; 14 ±2 years of education) and 25 heavy alcohol drinkers (33 ±9 years of age; 25 males; 13 ±2 years of education) using PET and ^{18}FDG both with (**VS)** and without (**NS**) visual/auditory stimulation (watching a video versus watching a blank screen). The NML participants had to have prior experience with alcohol but should not drink more than 1 drink/day. Inclusion criteria for HD was 4 (5) or more drinks/day if female (male) at least on 3 or more occasions per week. The HD reported their last use of alcohol was within 3 days of the PET scans. Fifteen of the 23 healthy controls, but none of the HD, were included as participants in the study that assessed the effects of alcohol intoxication on brain glucose metabolism to be compared with its effects on brain [^{11}C]acetate uptake (Volkow et al., 2013).

Alcohol and Placebo Administration and Stimulations Conditions: Participants were tested over a four day period; with placebo on two days (once with **NS** and once with **VS**) and with alcohol on the other two days (once with **NS** and once with **VS**). The order of drug and stimulation conditions was randomly assigned across subjects to control for

order effects. Subjects drank the alcohol (0.75 g/kg mixed in a caffeine-free diet soda) or the placebo (caffeine-free diet soda) beverages within a 20 minutes period under blind conditions. For this purpose, we used a specialized drinking container with an alcohol-containing lid that provided the smell of alcohol and delivered the same volume of liquid for both conditions. Participants were injected with ^{18}FDG 40 minutes after drinking onset (20 minutes after completion of drinking). This timing was selected to match the time for alcohol concentration to peak in the human brain after oral alcohol consumption (Hetherington et al., 1999). We used a 0.75 g/kg oral alcohol dose, which is roughly equivalent to three drinks for a 50 kg person and is within the range consumed by social drinkers (Stinson et al., 1998).

For the **NS** condition participants watched a blank computer screen whereas for the **VS** condition they watched a video that contained peaceful scenes showing normal people doing recreational activities (ie horseback riding, running in the park) that included the corresponding soundtracks (background noise but no conversations). Participants were exposed to the blank screen or the video starting at the time of ^{18}FDG injection and continued throughout the first 30 minutes of the ^{18}FDG uptake period while they rested comfortably in a quiet room. Participants were asked to keep their eyes open at all times to ensure they did not fall asleep during the procedures and a nurse remained by their side to ensure compliance. Thirty minutes after ^{18}FDG injections participants were positioned in the PET scanner for scanning.

Behavioral Evaluation and measures of Alcohol in Plasma: Before placebo or alcohol, and at 10, 15, 30 and 85 minutes after placebo or alcohol administration, subjects were asked to evaluate their subjective sense of “high” and at 15 and 100 minutes their sense of intoxication and desire for alcohol on analog scales (rated 1-10).

Blood alcohol concentration levels were measured before and 20, 40, 50, 80 and 100 min after the initiation of alcohol administration using the enzymatic assay described by Lloyd (Lloyd et al., 1978).

PET scans: Each participant underwent 4 PET-^{18}FDG scans done on separate days with the order of scans randomized: Placebo-**NS**, Placebo-**VS**, Alcohol-**NS** and Alcohol-**VS**. Scans were done using a Siemens ECAT EXACT HR+ tomograph. Participants were positioned in the scanner using their individual head holder. Transmission scans were obtained using germanium-68 to correct for attenuation. For the emission scans participants were injected with 4-6 mCi of ^{18}FDG and a twenty minutes emission scan was started 35 minutes after injections. Images were reconstructed using filtered back projection (Hann filter with a 4.9 mm Kernel FWHM). The ^{18}FDG scans were transformed into metabolic images as previously described (Volkow et al., 1990) and metabolic rates were computed using an extension of the Sokoloff's model (Phelps et al., 1979).

To ensure that subjects did not fall asleep they were monitored throughout the procedure and were asked to keep their eyes open. Subjects were scanned in a dimly lit room with noise kept to a minimum and the only intervention was the periodic assessment of the effects of alcohol or placebo.

Analysis: Statistical parametric mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK)(Friston et al., 1995) was used for the analysis. Gender and smoking status were entered as covariates to control for differences between the groups on these variables.

The absolute metabolic images were spatially normalized to the stereotactic space of the Montreal Neurological Institute (MNI) and resliced to 2 mm isotropic voxels using a 12 parameters affine transformation and the PET template included in the SPM package; subsequently, the images were smoothed using an 8-mm isotropic Gaussian kernel. A full factorial design with Group as between Factor (NML vs HD) and Drug (PL and Alcohol) and Condition (**NS** and **VS**) as within factors was used to assess: 1) if alcohol-induced metabolic changes differed between NML and HD when tested with **NS** and when tested with **VS;** and 2) if alcohol effects differed between **NS** and **VS**. We also compared the resting metabolic measures (placebo **NS**) between HD and NML to assess if these

differed between groups. The model included two zero-mean covariates controlling for effects of gender and smoking, variables that were significantly different for NML and HD. Significance was set as $P_{FWE} < 0.05$ corrected for multiple comparisons at the cluster level using the random field theory with a family wise error (FWE) correction, cluster forming threshold $P < 0.005$ and a minimum cluster size of 100 voxels. In addition to assessing the regional effects from video-stimulation we also used SPM to compare the relative metabolic images (normalized to whole brain) since relative measures increases the sensitivity to detect regional effects and significance set at $P_{FWE} < 0.05$. The measure of whole-brain metabolism was obtained by averaging the activity across the various axial planes in the brain.

RESULTS

Subjects Characteristics

The groups differed in gender composition, 9 females in NML group and 0 females in HD group (p=0.002) and in smoking histories, 7 HD were current smokers but 0 NML were smokers (p=0.02). To account for the group differences in gender and smoking we entered these two variables as covariates in the brain imaging comparisons between the groups.

As expected the groups differed in average daily alcohol consumption (quantified as beer equivalents per day), which in NML was 0.26 ±0.5 and in HD 8.6 ±3.4 (p< 0.0001).

Plasma Alcohol Concentration, Behavioral and Cardiovascular Effects

Plasma alcohol concentration did not differ between NML and HD or between the **NS** and **VS** conditions (Figure 1A and 1B).

Alcohol increased self-reports of "high" (**NS** F=27, p< 0.0001, **VS** F=31, p<0.0001), "intoxication" (**NS** F=125 p=0.0001; **VS** F=72, p<0.0001) and "desire for alcohol" (**NS** F=5.1, p=0.008; **VS** F=7.7, p=0.0008). Alcohol-induced behavioral measures did not differ between groups (Figure 1C and 1D). Across all time measures "desire for alcohol" was higher for HD than NML (**NS** F=7.7 p=0.02, **VS** F=6.8 p=0.02).

Effects of Alcohol on Brain Glucose Metabolism During NS and VS.

The statistical parametric mapping (SPM) analysis (p_u<0.005) revealed that acute alcohol significantly decreased whole-brain glucose metabolism in NML and HD for both **NS** and **VS** (Figure 2, Table 1). The occipital cortex was the region that showed the largest decrements across both groups. Subcortical regions (striatum, thalamus and midbrain) did not show significant decrements except for the thalamus in HD (Figure 2, Table 1). In both NML and HD alcohol-induced decrements in metabolism were more extensive for **NS** than for **VS** (Figure 2).

The group by condition interaction was not significant for any of the brain regions indicating that the effects of **VS** on alcohol-induced metabolic decrements did not differ between groups.

Plasma alcohol levels did not show significant correlation with alcohol-induced changes in brain glucose metabolism.

Differences between NML and HD

The SPM analysis assessing group differences in resting brain glucose metabolism (placebo-**NS**) showed that NML had significantly higher metabolism than HD (Figure 3). Whole-brain metabolic values corresponded for the NML to 38.6 ±6 micromol/100g/min and for the HD to 33.6 ±6 micromol/100g/min (group difference, $p < 0.01$).

The SPM analysis to assess group differences in alcohol effects showed that alcohol-induced metabolic decreases were more extensive in HD than in NML and were larger in thalamus, frontal and temporal cortices in HD than NML (Figure 2). Whole-brain metabolism was reduced by alcohol during **NS** by 9.3 ±11 percent (change from placebo) in NML and 19.8 ±13 percent (group difference, $p <0.005$) in HD; and during **VS** it was reduced by 6.1 ±13 percent in NML and 13.6 ±12 percent in HD (group difference $p < 0.05$).

Daily alcohol consumption showed significant correlation with the decreases in whole-brain glucose metabolism for **NS** (r=0.42, p=0.003) and a trend for **VS** (r=0.27, p=0.06).

E**ffect of Alcohol on VS-induced Increases in Visual Cortical Metabolism** Since the effect of **VS** on brain glucose metabolism was not significantly different between HD and NML in any brain region we combined both groups to increase statistical power.

Video-stimulation (**VS** vs **NS**) increased glucose metabolism in the visual cortex (BA 18) during placebo and in visual (BA 18) and auditory (left BA 22) cortices during alcohol intoxication (Figure 4, Table 2). Though the effects of **VS** in the visual cortex tended to be larger during alcohol intoxication than during placebo, this effect was not significant after correction for multiple comparisons.

To assess the effects of **VS** on regional brain metabolism we also computed its effects on the "relative" metabolic images (normalized to whole-brain metabolism) to enhance regional over global effects. SPM on the "relative" metabolic images revealed significant **VS**-induced increases in visual and auditory cortices both during placebo and during alcohol intoxication (Figure 5). There were no differences on **VS**-induced increases in "relative" metabolism between placebo and alcohol intoxication.

DISCUSSION

Here we show 1) a marked decrease in brain glucose metabolism during alcohol intoxication that was significantly greater in HD than NML; 2) that alcohol intoxication despite inducing marked decrements in whole brain glucose metabolism during rest did not reduce increases in regional glucose metabolism during stimulation (**VS**); and 3) that **VS** reduced the magnitude of the decrements in brain glucose metabolism induced by alcohol intoxication. We also show that resting brain glucose metabolism was significantly lower for HD than for NML.

Alcohol-induced decreases in brain glucose metabolism were larger for HD than for

NML. The reductions in brain glucose metabolism during alcohol intoxication corroborate prior findings of decrements in brain glucose metabolism during intoxication that as for the current study were largest in occipital cortex and smallest in subcortical brain regions (reviewed (Volkow et al., 2006)) including our recent findings showing an opposite pattern between the regional increases in acetate metabolism and the regional decreases in brain glucose metabolism (Volkow et al., 2013). Our findings of significantly larger brain metabolic decrements with alcohol intoxication in HD than in NML, is consistent with our pilot study that reported significantly larger reductions in brain glucose metabolism with alcohol in alcoholics (n=6) than in controls (n=6) despite alcoholics being less intoxicated than the controls (Volkow et al., 1990).

Alcohol-induced reductions in brain glucose metabolism could reflect either the GABAergic enhancing effects of alcohol (Wang et al., 2000; Roberto et al., 2003; Rae et al., 2014) and/or the use of acetate (or other ketone bodies) as an alternative energy substrate during intoxication (Pawlosky et al., 2010). Our current findings suggest that they reflect the use of an alternative energy source. First, the higher metabolic reduction in HD than in NML is compatible with the use of alternative energy sources during intoxication since alcohol abusers show attenuated reductions in brain glucose metabolism when given GABAergic enhancing drugs (Volkow et al., 1993; Volkow et al., 1997) rather than an enhanced reduction as shown here. Second, the lower sensitivity to alcohol-induced metabolic decreases in the thalamus, which was also the region that was less sensitive to the increases in acetate metabolism during intoxication (Volkow et al., 2013) but the most sensitive to the decrements in glucose metabolism triggered by GABAergic enhancing drugs (Volkow et al., 1995), is also consistent with alcohol-induced use of acetate as an alternate energy substrate. The thalamus might have been the least sensitive region to the effects of alcohol in glucose and acetate metabolism because the expression of monocarboxylic acid transporters, which transport acetate into asytrocytes (Pellerin et al., 1998) and the levels of acetyl-CoA synthetase, which is an enzyme needed for acetate oxidation, are low (Qin and Crew 2014). Thus our findings are consistent with the hypothesis that the reduction in brain glucose metabolism during intoxication is due to increased metabolism of alternative energy substrates (presumably

acetate) and that chronic alcohol exposure facilitates this shift.

Acetate is readily taken up by the brain and metabolized by glia (Cruz et al., 2005). Under normal physiological conditions plasma acetate levels are low (about 0.2 to 0.3 mM) but during intoxication the blood concentration of acetate increases (around 1 mM) (Orrego et al., 1988) to levels that could support 10-20% of total brain metabolic rate (Waniewski and Martin, 1998). Moreover during intoxication the blood acetate concentrations are higher for alcoholics than for controls (Nuutinen et al., 1985), which could facilitate metabolism of acetate by glial cells, as shown for laboratory animals chronically exposed to alcohol (Wang et al., 2013a; Wang et al., 2013b). Figure 6 summarizes the interpretation of our findings.

Though we interpret the enhanced reduction in glucose metabolism during intoxication in HD to reflect a priming for their metabolism of acetate, in a prior study in which we reported increases in brain acetate metabolism during intoxication (measured with [^{11}C]acetate and PET) we showed no differences between controls and HD (Volkow et al 2013). However, overall brain acetate metabolism in the HD tended to be higher than in controls particularly for the scans taken during intoxication and was associated with their alcohol histories, consistent with priming for the use of acetate as brain energy substrate in HD (Volkow et al 2013). Alternative the discrepancy between the current and our prior study could indicate that acetate might not be the only alternative energy substrate used by the brain during intoxication.

Alcohol did not reduce glucose metabolic increases in visual cortex from video-stimulation. Despite the marked reductions in brain glucose metabolism during intoxication the increases in glucose metabolism in visual cortex (and auditory cortex) triggered by **VS** were not decreased by alcohol when compared to placebo. This indicates that the increased energy required by the stimulation is dependent on glucose.

Indeed, stimulations that increase energy demand require additional increases in glucose metabolism by neurons and glia (Kasischke et al., 2004). Furthermore, there is evidence

that task-induced changes in regional brain activity are associated with increases in aerobic glycolysis (glucose utilization that is in excess of its use for oxidative phosphorylation despite sufficient oxygen) (Fox et al., 1988; Vlassenko et al., 2006), which could account in part for the reliance on glucose during brain stimulation. Intriguingly, there is also evidence of generation of ATP through glycolytic metabolism in dendritic spines during synaptic signaling that might also underlie the need of glucose from brain stimulation (Wu et al., 1997).

VS attenuated alcohol-induced decrements in brain glucose metabolism.

The attenuated effects of alcohol during **VS** are consistent with the preferential upregulation of glycolysis during activation (Dienel et al., 2001). The fact that during stimulation neurons require immediate access to glucose, which is predominantly processed through the anaerobic cycle, could explain why we observed an attenuation of alcohol-induced decrements in brain glucose metabolism during the **VS** condition.

Brain glucose metabolism at baseline (placebo-NS) was lower in HD than NML

The lower brain glucose metabolism in the HD compared to NML (placebo-**NS**) is consistent with the findings that alcoholics have significant reductions in brain glucose metabolism when compared with healthy controls (Samson et al., 1986; Gilman et al., 1990; Martin et al., 1992; Volkow et al., 1992; Adams et al., 1993; Wang et al., 1993). Though the reductions in regional brain glucose metabolism in alcoholics could reflect neurotoxicity these reductions have also been reported in neurologically intact healthy alcoholics (Volkow et al., 1992) indicating that they could also reflect reliance on alternative energy substrates for brain metabolism. Since most findings tested alcoholics during early detoxification it suggests that reliance on alternative energy substrates for brain metabolism may persist after intoxication has subsided. Indeed a recent MRS study showed significantly enhanced acetate metabolism in the occipital cortex of heavy drinkers studied during sobriety (Jiang et al., 2013). Persistent reliance on brain acetate metabolism for energetics during early alcohol detoxification could also explain why reductions in brain glucose metabolism in alcoholics mostly recover within the first 2 weeks of detoxification (Volkow et al., 1994) and why female alcoholics who were

studied in average 30 days after detoxification showed no abnormalities in brain glucose metabolism (Wang et al., 1998).

Clinical implications

Our current findings along with those from prior studies (Jiang et al., 2013; Volkow et al., 2013; Wang et al., 2013b) indicate that with chronic alcohol exposure the brain increasingly relies on acetate (perhaps also other energy substrates) for metabolism. This is likely to have clinical implications for the management of alcohol use disorders. Specifically during acute alcohol withdrawal the associated drop in acetate plasma levels might result in a sudden deprivation of a favored energy substrate that could result in brain energy deprivation and contribute to the adverse effects of alcohol withdrawal in alcohol abusers. In fact energy deprivation had previously been proposed to contribute to the emergence of alcohol withdrawal during alcohol discontinuation (Derr, 1984) and in rodents acetate infusion abated the signs of ethanol withdrawal (Derr et al., 1981). This raises the possibility that a ketogenic diet by providing a high level of acetone could help minimize adverse effects from acute alcohol withdrawal in alcohol abusers undergoing detoxification.

Limitations

It would have been desirable to measure plasma acetate concentrations both at baseline and during intoxication, which would have allowed us to assess if the lower baseline brain metabolic measures in the HD reflected higher plasma acetate levels and to assess the correlations between alcohol-induced increases in plasma acetate levels during intoxication and the reductions in brain glucose metabolism. Future mechanistic studies including these measures merit consideration.

Summary

We show that alcohol markedly reduces brain glucose metabolism at baseline but does not interfere with the increases in metabolism from activation, which indicates that the shift in alternative energy substrates relates to resting activity only (presumably glia support of baseline activity) and not to energy requirements for stimulation (presumably

glucose to support neuronal and glial activation). We also show that HD have an enhanced reduction in glucose metabolism with alcohol intoxication consistent with their brain being more adept at using alternative energy substrates (presumably acetate) secondary to chronic alcohol exposures.

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Figure Legends

Figure 1. Alcohol levels in plasma and self-reports for drug effects after placebo (PL) and after alcohol (ALC) for the no-stimulation (**NS**) and for the video stimulation (**VS**) conditions in heavy drinkers (HD) and in normal controls (NML). A. Plasma alcohol concentration did not differ between NML and HD either for **NS** or **VS**. B. Alcohol significantly increased self-reports of high and intoxication both for **VS** and **NS** but did not increase desire for alcohol. The groups differed only on 'Desire for alcohol" which was significantly higher for HD than NML. Alcohol behavioral effects did not differ between groups.

Figure 2. Effects of alcohol on brain glucose metabolism in normal controls (NML) and heavy drinkers (HD). A. SPM results showing areas where the absolute metabolic measures were significantly reduced by alcohol when compared to placebo (PL > ALC) for the no-stimulation (**NS**) and the video-stimulation (**VS**) in NML and HD at $p_{FWE}<0.005$. B. Histogram showing regions where effects of alcohol where greater during **NS** than **VS**.

Figure 3. Differences in baseline brain glucose metabolism (placebo measures) between normal controls (NML) and heavy drinkers (HD). A. SPM results showing areas where metabolism was significantly greater for NML than HD (NML > HD) at $p_{FWE}<0.0001$. B. Histogram showing brain metabolism in BA 18 and BA 22 for the placebo conditions; these areas also showed greater metabolic values in NML than HD

Figure 4. Effects of video-stimulation (**VS**) on brain glucose metabolism (absolute metabolic images) when compared with no –stimulation (**NS**) during placebo (PL) and alcohol intoxication (ALC). A. SPM results showing areas where metabolism was greater for **VS** > **NS** for significance $p_{FWE}<0.05$. There were no areas where metabolism was greater for NS than for VS. B. Histograms showing the differences (**VS** versus **NS**)

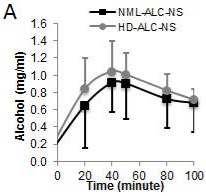
in metabolic rates in BA 18 and BA 22, for the combined PL & ALC for NML and HD.

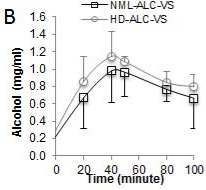
Figure 5. Effects of video-stimulation (VS) on relative metabolic images (normalized to whole brain metabolism) during placebo (PL) and alcohol intoxication (ALC). A. SPM results showing areas where "relative metabolism" was greater for VS > NS for significance $p_{FWE}<0.05$. B. Histograms showing "relative" metabolic values in BA 18 and BA 22, for NML and for HD, during the PL and ALC conditions.

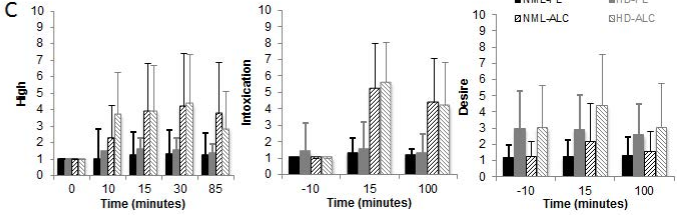
Figure 6. Simplified model for the interpretation of our findings. In sobriety, glia and neurons predominantly rely on glucose as energy substrate for metabolism at rest and during stimulation, both through aerobic glycolysis and through oxidative phosphorylation. During alcohol intoxication (acute alcohol), when acetate levels in plasma increase, glial cells increase their reliance on acetate metabolism as energy source to sustain resting activity. In heavy drinkers, the reliance of glial cells on acetate to sustain resting activity is enhanced and persists beyond intoxication, which could contribute to their low resting brain glucose metabolic rates during sobriety but also their larger decrements in brain glucose metabolism during intoxication,

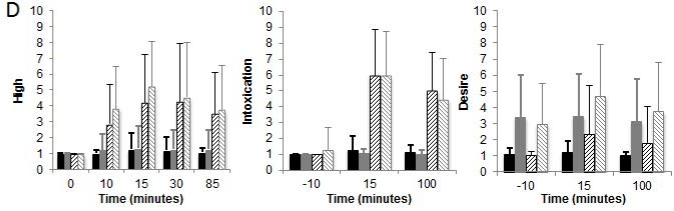
Table 1: SPM results for the differences between Placebo and Alcohol. Table shows statistical significance (t-score), and the spatial location of the clusters showing significant differences in absolute glucose metabolism between placebo (PL) and alcohol (ALC) conditions under visual stimulation (**VS**) and no stimulation (**NS**) for heavy drinkers (HD) and matched controls (NML).

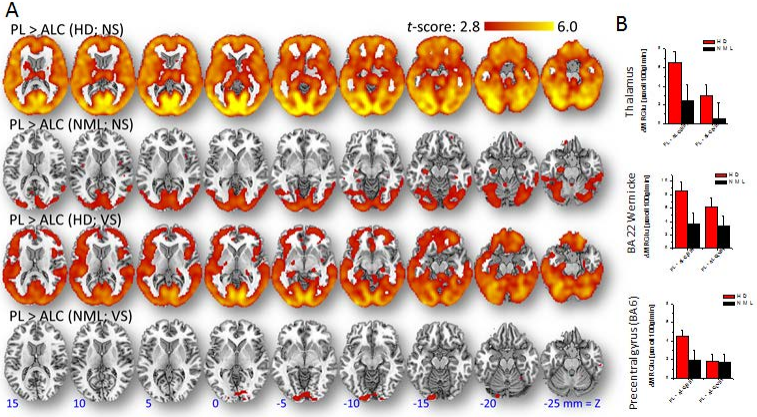
Table 2: SPM results for comparison on brain glucose metabolism between visual stimulation (**VS)** and no stimulation (**NS**). Table shows the statistical significance (t-score) and spatial location of the clusters showing significant differences in absolute glucose metabolism between **VS** and **NS**, for alcohol (ALC) and placebo (PL) conditions, across all subjects (NML & HD conjunction analysis).

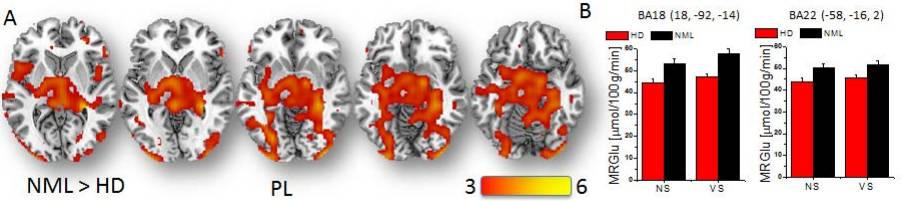

A
NML-ALC-NS
HD-ALC-NS
Alcohol (mg/ml)
Time (minute)

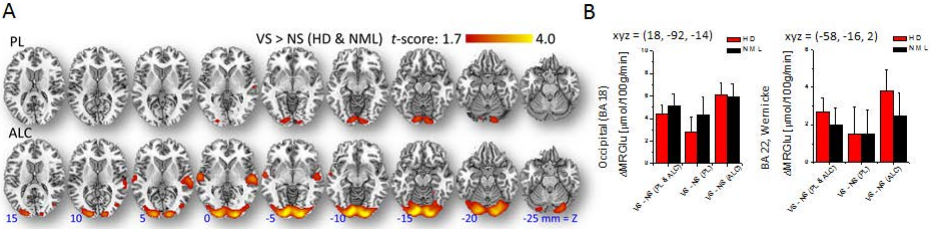

B
NML-ALC-VS
HD-ALC-VS
Alcohol (mg/ml)
Time (minute)

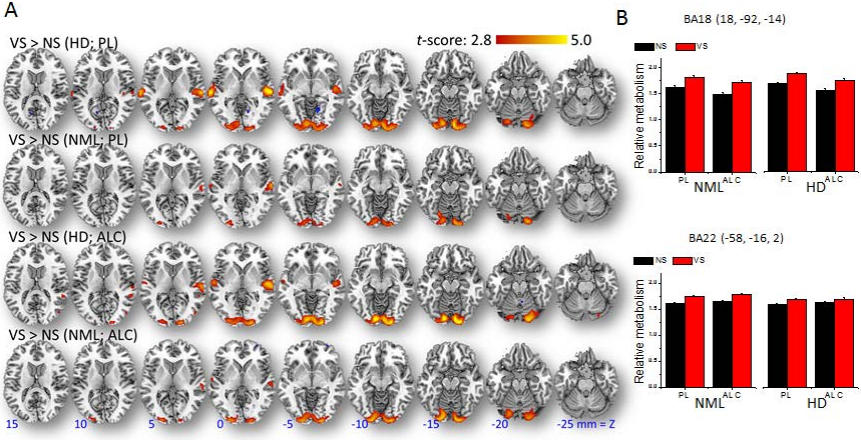

C
NML-PL
HD-PL
NML-ALC
HD-ALC
High
Intoxication
Desire
Time (minutes)

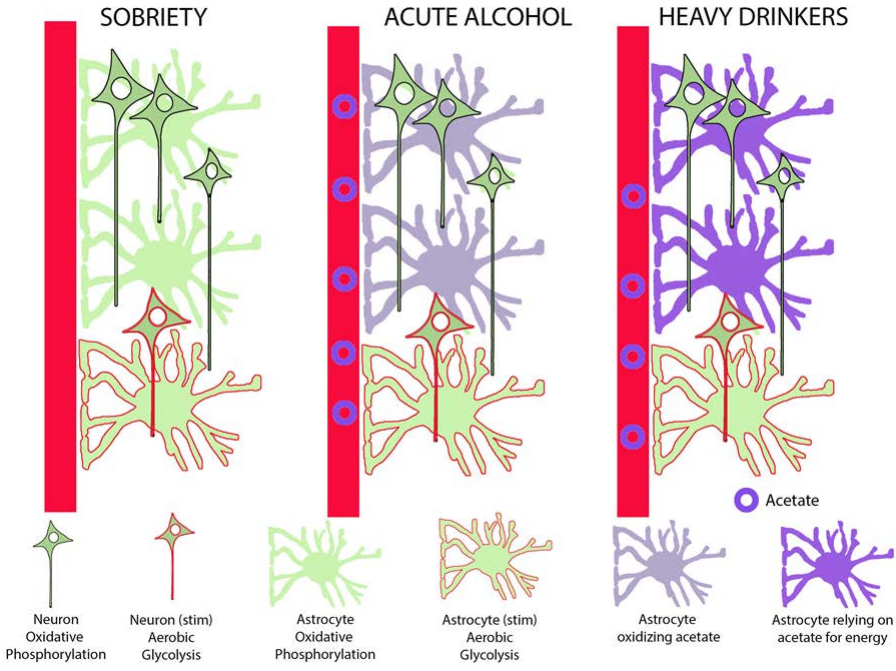

D
High
Intoxication
Desire
Time (minutes)


A
PL > ALC (HD; NS)
t-score: 2.8
6.0
PL > ALC (NML; NS)
PL > ALC (HD; VS)
PL > ALC (NML; VS)
15
10
5
0
-5
-10
-15
-20
-25 mm = Z
B
Thalamus
BA 22 Wernicke
Precentral gyrus (BA6)
HD
NML


A
NML > HD
PL
3
6
B
BA18 (18, -92, -14)
BA22 (-58, -16, 2)
HD
NML
MRGlu [µmol/100g/min]
NS
VS


A
PL
ALC
VS > NS (HD & NML) t-score: 1.7
4.0
15
10
5
0
-5
-10
-15
-20
-25 mm = Z
B
xyz = (18, -92, -14)
HD
NML
Occipital (BA 18)
ΔMRGlu [μmol/100g/min]
VS - NS (PL & ALS)
VS - NS (PL)
VS - NS (ALS)
xyz = (-58, -16, 2)
BA 22, Wernicke


A
VS > NS (HD; PL)
t-score: 2.8
5.0
VS > NS (NML; PL)
VS > NS (HD; ALC)
VS > NS (NML; ALC)
15
10
5
0
-5
-10
-15
-20
-25 mm = Z
B
BA18 (18, -92, -14)
NS
VS
Relative metabolism
PL
ALC
NML
HD
BA22 (-58, -16, 2)


SOBRIETY
ACUTE ALCOHOL
HEAVY DRINKERS
Acetate
Neuron
Oxidative
Phosphorylation
Neuron (stim)
Aerobic
Glycolysis
Astrocyte
Oxidative
Phosphorylation
Astrocyte (stim)
Aerobic
Glycolysis
Astrocyte
oxidizing acetate
Astrocyte relying on
acetate for energy

Region	BA	MNI coordinates [mm]			PL > ALC (NS)		PL > ALC (VS)	
		x	y	z	HD	NML	HD	NML
Calcarine	17	-8	-82	0	7.2	3.7	5.6	2.3
Calcarine	17	12	-70	6	7.0	3.4	4.9	2.2
Cerebellum		-40	-64	-40	6.8	3.8	4.1	2.6
Cerebellum		-22	-78	-36	6.6	3.4	4.0	2.9
Vermis		6	-70	-36	6.6	3.1	4.2	2.4
Superior Occipital	18	-20	-90	22	6.3	3.0	4.1	NS
Cerebellum		36	-72	-22	6.1	3.8	5.3	2.2
Fusiform	37	30	-54	-18	6.1	3.3	4.8	2.7
Middle Occipital	19	-40	-84	0	6.0	3.1	4.4	1.9
Inferior Frontal	44	-48	10	24	5.7	2.5	3.9	1.6
Superior Orbitofrontal	11	-18	38	-22	5.6	2.5	4.1	2.2
Middle Frontal	47	-38	46	0	5.4	2.2	3.3	1.8
Inferior Temporal	20	-52	-10	-26	5.3	2.1	3.8	NS
Inferior Temporal	20	64	-44	-14	5.3	3.0	3.7	2.2
Middle Cingulum	23	2	-38	34	5.2	2.7	3.5	1.7
Middle Occipital	39	48	-74	24	5.2	2.6	3.7	1.9
middle Orbitofrontal	11	30	42	-16	5.2	2.8	4.6	2.0
Inferior Frontal	45	52	30	4	5.2	2.6	3.4	2.0
Superior Temporal	41	-42	-28	8	5.1	2.0	4.3	NS
SupraMarginal	42	-58	-24	18	5.1	1.7	3.3	NS
Superior Frontal	10	-24	58	2	5.1	2.0	3.3	1.7
Angular	7	38	-74	40	5.1	2.8	3.5	2.4
Inferior Frontal	6	56	10	10	5.1	2.6	2.9	2.1
Superior Frontal	10	24	56	14	5.1	2.4	3.2	1.9
Angular	39	-50	-62	24	5.1	2.1	3.8	1.7
Superior Temporal	22	52	-24	8	5.1	2.6	3.6	1.9
Inferior Temporal	20	58	-30	-24	5.1	3.1	3.5	2.5
Precentral	44	48	6	34	5.0	2.7	3.7	2.0
Superior Temporal	42	-54	-42	18	5.0	2.2	3.2	NS
Middle Frontal	9	-30	40	36	5.0	NS	2.5	NS
Inferior Parietal	3	-52	-26	50	4.7	1.9	2.4	NS
Precentral	6	-36	2	56	4.7	2.0	3.0	NS
Middle Cingulum	32	8	36	30	4.5	2.0	2.6	NS
Middle Frontal	8	-24	12	56	4.4	1.9	2.9	NS
Precentral	6	38	-8	56	4.3	1.7	2.6	NS
Thalamus	0	14	-18	8	4.3	NS	2.7	NS

Region	BA	MNI Coordinates [mm]			VS > NS	
		x	y	z	ALC	PL
Lingual	18	14	-90	-12	4.5	2.3
Inferior Occipital	18	-20	-96	-6	4.3	1.8
Superior Temporal	22	-58	-20	2	3.0	1.8
Superior Temporal	22	60	-12	0	2.7	NS