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# Positive Emotionality is Associated with Baseline Metabolism in Orbitofrontal Cortex and in Regions of the Default Network

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## Abstract

Positive Emotionality (personality construct of well being, achievement/motivation, social and closeness) has been associated with striatal dopamine D2 receptor availability in healthy controls. Since striatal D2 receptors modulate activity in orbitofrontal cortex and cingulate (brain regions that process natural and drug rewards) we hypothesized that these regions underlie positive emotionality. To test this we assessed the correlation between baseline brain glucose metabolism (measured with positron emission tomography and [$^{18}$F]fluoro-deoxyglucose) and scores on Positive Emotionality (obtained from the Multidimensional Personality Questionnaire or MPQ) in healthy controls (n=47). SPM analyses revealed that Positive Emotionality was positively correlated ($p_c$<0.05, voxel corrected) with metabolism in various cortical regions that included orbitofrontal (BA 11, 47)

and cingulate (BA 23, 32) and other frontal (BA 10, 9), parietal (precuneus, BA 40) and temporal (BA 20, 21) regions that overlap with the brain's default mode network. Correlations with the other two main MPQ personality dimensions (Negative Emotionality and Constraint) were not significant (SPM $p_c<0.05$). Our results corroborate an involvement of orbitofrontal and cingulate regions in positive emotionality, which is considered a trait that protects against substance use disorders. Since dysfunction of orbitofrontal cortex and cingulate is a hallmark of addiction these findings support a common neural basis underlying protective personality factors and brain dysfunction underlying substance use disorders. In addition we also uncovered an association between Positive Emotionality and baseline metabolism in regions from the default mode network, which suggests that Positive Emotionality may relate to global cortical processes that are active during resting conditions (introspection, mind wandering).
**Keywords:** rectal gyrus, vulnerability, FDG, brain imaging, prefrontal cortex, personality, addiction
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## Introduction

The investigation of the neurobiological processes underlying personality characteristics may help understand the mechanisms by which personality can increase or decrease the risk for psychopathology[1]. For substance abuse disorders (SUD) personality traits associated with greater vulnerability include impulsivity, novelty seeking and negative emotionality whereas the personality trait of positive emotionality is associated with resilience[2]. Understanding the neurobiological mechanisms by which positive emotionality may provide resilience against SUD would help develop strategies to emulate this for SUD prevention. However, the mechanisms by which positive emotionality may protect against SUD are unclear but are likely to reflect a common neurobiological substrate underlying this personality trait and its dysfunction in SUD.

Individuals with high scores on positive emotionality have high reward sensitivity, are motivated and have a propensity to experience positive moods (i.e., joy, enthusiasm). Dopamine (DA), which is a neurotransmitter involved with reward and motivation, has been implicated in positive emotionality[3,4]. DA is also recognized to play a crucial role in the reinforcing effects of drugs and in the neuroadaptations that result in addiction (review[5]). Thus dopaminergic pathways could underlie a common substrate for positive emotionality and SUD. Indeed, brain imaging studies have documented an association between high striatal D2 receptor availability and high scores on

positive emotionality[6], and between high striatal D2 receptors and a greater resilience against the reinforcing effects of stimulant drugs in humans[7,8] and compulsive administration in rodents[9]. In contrast, low striatal D2 receptor levels have been associated with a greater vulnerability to drug self-administration in laboratory animals[10] and with SUD in humans (review[5]).

The involvement of DA in positive emotionality is believed to be mediated in part via its regulation of prefrontal cortical regions including orbitofrontal cortex OFC and anterior cingulate gyrus (ACC)[3,4]. Indeed, since striatal D2 receptors are associated with metabolism in OFC and ACC (reviewed[5]), we postulated that the association between positive emotionality and striatal D2 receptors in healthy controls was mediated through the OFC and ACC. The OFC and ACC encode salience attribution of rewards[11,12] including social[13,14] and drug rewards[15] and the ACC is also involved in the representation of affective value[14]. These regions are also crucial for inhibitory/impulse control and emotion regulation. Thus differing activity of these regions could underlie differing sensitivity to rewards and differing emotional reactivity among individuals. Indeed, there is recent evidence linking gray matter density in the OFC and scores on the personality measure of social reward dependency[16].

Here we test the hypothesis that the OFC and ACC are involved in the personality trait of positive emotionality. Specifically, we investigated whether baseline glucose metabolism, a marker of brain function[17], in the OFC and ACC was associated with positive emotionality. Brain glucose metabolism was measured using positron emission tomography (PET) and [$^{18F}$]fluoro-deoxyglucose (FDG) under baseline conditions (awake, eyes open, no stimulation) in healthy subjects (n=47). Positive Emotionality was assessed using the Multidimensional Personality Questionnaire (MPQ)[18]. We also assessed the correlations between brain glucose metabolism and the other two main personality dimensions from the MPQ (Negative Emotionality and Constraint) as a control against which to evaluate the specificity of any correlations found with Positive Emotionality.

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## Material and Methods

### Subjects

The forty-seven healthy controls reported in this study were participants in two separate protocols. One study recruited 23 healthy participants (Study 1, unpublished data; 12 F, 30 ± 9 years of age, 2 smokers) and the other included the baseline data from 24 healthy participants from a previously published

study (Study 2, 12 F, 33 ± 7 years of age, 5 smokers)[19]. The demographic profiles of the subjects were similar for both studies. Subjects were recruited using public advertisement seeking healthy volunteers, who were initially screened by phone and subsequently evaluated for eligibility by a physician. Subjects were excluded if they had current or past psychiatric disorders (including drug abuse or dependence), neurological diseases, significant medical illnesses, were currently on medication(s) (including over the counter drugs) or were pregnant. As part of the evaluation procedure, subjects had a physical, psychiatric and neurologic examination. Routine laboratory tests were performed as well as a urine test to rule out the use of psychoactive drugs. Subjects were instructed to discontinue any over-the-counter medications two weeks prior to the PET scan and to refrain from drinking alcohol the week prior to the PET scan. Cigarettes, food, and beverages (except for water) were discontinued at least 4 hours prior to the study. The studies were approved by the local Institutional Review Board (Committee on Research Involving Human Subjects, Stony Brook University). After explaining the procedure, written informed consent was obtained from each subject.

### Personality measures

Participants completed the Multidimensional Personality Questionnaire[18]. The personality measures were scored for the 3 main personality dimensions of the MPQ: Positive Emotionality (or extraversion), Negative Emotionality (or neuroticism) and Constraint. The Positive Emotionality (PEM) includes measures of well-being, social potency, achievement (including motivation) and social closeness. The Negative Emotionality (NEM) includes measures of stress reactivity, alienation, and aggression. The Constraint factor includes measures of self-control, harm avoidance and traditionalism.

### PET Studies

PET studies were carried out with an HR+ tomograph (resolution 4.5×4.5×4.5 mm full width half-maximum, 63 slices) in 3D dynamic acquisition mode. Subjects were scanned under baseline conditions with FDG as described[20]. Briefly, a 20 minutes emission scan was started 35 minutes after injection of 4-6 mCi of FDG, and arterialized blood was used to measure FDG in plasma. During the uptake period of FDG subjects were resting (no stimulation) in a quiet dimly lit room (eyes open) with a nurse by their side to ensure that they did not fall asleep. Thirty minutes after FDG injection subjects were positioned in the PET scanner. Metabolic rates were computed using an extension of Sokoloff's model[21]. The emission data for all the scans were corrected for attenuation and reconstructed using filtered back projection.

### Image Analysis and Statistics

The data were analyzed both using Statistical Parametric Mapping (SPM)[22]and independently drawn regions of interest (ROI). The SPM analysis was performed on the images from all subjects (n=47) and the results were then subsequently corroborated for each of the two studies separately. For SPM analysis, the metabolic images were spatially normalized using the template provided in the SPM 99 package and subsequently smoothed with a 16 mm isotropic Gaussian kernel. Voxel-wise correlations were obtained between absolute glucose metabolism and the PEM scores (a priori set measure) and the scores in the NEM and Constraint factors (to control for specificity in the correlations between regional metabolism and PEM). The threshold of significance was ser to $p_{corr} < 0.05$, corrected for multiple comparisons with the random field theory[23]. Clusters (> 100 voxels) that were significant were overlaid on a magnetic resonance image (MRI) of the human brain. For the analysis done on each separate study we set the SPM threshold of significance to $p < 0.005$, uncorrected cluster > 100 voxels.

For ROI analysis, we extracted independently drawn ROIs using an automated extraction method that is based on the standard Talairach atlas[24]. First, [$^{18}$F]FDG images were mapped onto the Talairach brain using the SPM99 spatial normalization algorithm. The inverse mapping procedure was used to extract the Talairach coordinates of all voxels for a given anatomical region using the stereotaxtic coordinates in the Talairach Daemon database[25]. These anatomically defined ROIs were overlapped voxel-by-voxel onto the SPM normalized PET image. These independently extracted ROIs were used to corroborate the significance ($p<0.05$) of the correlations between the personality measures and metabolism in the areas identified by SPM. Only findings that were significant both by SPM and by the independently extracted ROIs were considered significant.

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## Results

The scores of the personality measures did not differ between the subjects of the two separate studies. The average PEM scores were 49 ±11 (Study 1: 52 ±13 and Study 2: 47 ±9); the average NEM scores were 13 ±8 (Study 1: 12 ±9 and Study 2: 13 ±6), and the average Constraint factor scores were 51 ± 10 (Study 1: 52 ±11 and Study 2: 51 ±10).

The SPM analyses revealed a significant correlation between PEM and baseline metabolism in a broad range of cortical regions. To determine significance we used a family-wise error (FWE) threshold $P < 0.05$, corrected for multiple comparisons at the voxel level (Figure 1). This identified 8

clusters, all of which remained significant after the conservative FWE corrections for multiple comparisons (Table 1). These clusters were located in areas that included the left and right OFC and ACC but also identified additional areas in middle and lateral frontal (BA 9, 10), temporal gyrus (BA 20, 21, 22), parietal (precuneus, BA 7, 40) and in left and right occipital cortex (fusiform gyrus and superior occipital gyrus). Many of these regions are part of the default mode network (DMN) so to assess the degree of overlap we identified the location of the regions with positive correlations with PEM in a brain surface rendering where we projected the locations of the regions from the DMN and from the attention dorsal network (DAN) as described by Buckner26 (Figure 2). This identified significant overlap with DMN and minimal overlap with DAN.

Figure 1

Statistical Parametric Mapping (SPM) images identifying areas were metabolism was positively correlated with scores on positive emotionality (PEM). Significance corresponds to a family-wise error (FWE) threshold $p < 0.05$, corrected for multiple **...**

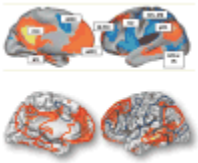

Figure 2

A. Location of regions in the medial and lateral surface of the left hemisphere that are part of the brain default mode network or DMN (red) that is most active in passive task settings and of regions that are part of the dorsal attention network or DAN **...**

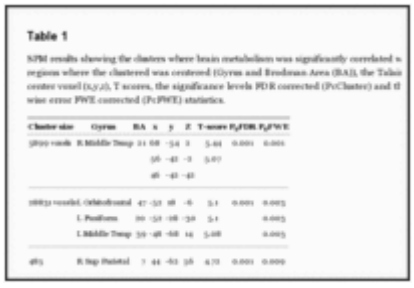

Table 1

SPM results showing the clusters where brain metabolism was significantly correlated with PEM, along with the regions where the clustered was centered

(Gyrus and Brodman Area (BA)), the Talairach stereotactic coordinate for center voxel (x,y,z), T scores, **...**

Correlation analysis between PEM and the metabolic measures computed with independently extracted ROI corroborated significance for all the regions identified by SPM (Table 2, Figure 3). This analysis also revealed a significant positive correlation with whole brain metabolism (r= 0.49, p < 0.001).

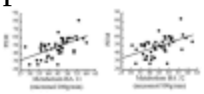

Figure 3

Regression slopes for the correlation between brain metabolism in orbitofrontal cortex (BA 11) and PEM (r = 0.58, p < 0.0001) and between metabolism in cingulate gyrus (BA 32) and PEM (r = 0.53, p < 0.0001). The regressions correspond **...**

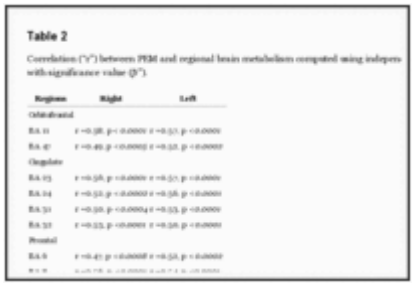

Table 2

Correlation ("r") between PEM and regional brain metabolism computed using independent ROI analysis along with significance value ("*p*").

The SPM voxel wise correlation analysis and the independent ROI analysis done separately for the subjects form Study 1 and those from Study 2 corroborated the findings from the analysis done in the complete study sample (Supplemental Figure 1 and Supplemental Tables 1 and 2).

The SPM correlations with the NEM or the Constraint factors were not significant ($p_c$<0.05). The threshold of significance had to be lowered to p < 0.01 (uncorrected), to detect any associations. For NEM, SPM (p<0.01, uncorrected) revealed a negative correlation with metabolism in right thalamus and superior medial frontal gyrus (Supplemental Figure 2). The ROI analysis corroborated the negative correlation in right thalamus for middle dorsal (r =0.41, p < 0.005) and ventral anterior nuclei (r=0.46, p < 0.001) but not in superior medial frontal gyrus. For the Constraint Factor, SPM (p<0.01, uncorrected) revealed a positive correlation with metabolism in caudate (Supplemental Figure 3). The ROI analysis corroborated the positive correlation in left caudate (r = 0.41, p < 0.004) and a trend in right caudate (r= 0.39. p < 0.008).

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## Discussion

These findings corroborate our hypothesis of an involvement of the OFC and the ACC in the disposition to positive emotionality. However, the positive correlations with PEM were not restricted to the OFC (BA 11, 47) and ACC (BA 23, 32) but encompassed a wides range of cortical regions that included other areas from middle and lateral frontal (BA 9, 10, 23), precuneus (BA 7, 31), parietal (BA 40) superior and middle temporal (BA 20, 21, 22) and fusiform cortices. Note that many of these cortical regions were located within the DMN (Figure 2).

The positive association between PEM and metabolic activity in medial and lateral OFC and in ACC in healthy controls is consistent with our findings in non-substance abusing subjects with a family history of alcoholism, in whom we also reported a positive correlation between PEM and baseline metabolic activity in OFC (BA 11, 25 and 47) and ACC (BA 24, 32)[6]. These results are also in good agreement with those reported in healthy controls in whom the trait of social reward dependency, which relates to the PEM measure of social closeness, was associated with increased gray matter density in OFC (also basal ganglia and temporal lobes)[16] and those in healthy women in whom extraversion, which relates to the PEM measure of social potency, was associated with OFC metabolism[27]. Similarly in healthy adults persistence, which relates to the PEM measure of achievement, was associated with OFC activation[28], and in adolescents higher effortful control, which also relates to achievement, was associated with larger OFC volume whereas higher affiliativeness, which relates to the PEM measure of social closeness, was associated with larger ACC volume[29].

The OFC and the ACC are involved in motivation and reward[30], social behaviors[31] and emotional regulation[32], all of which are processes that contribute to the personality trait of positive emotionality. Indeed, case studies have reported that damage to these brain regions in premorbidly normal patients resulted in personality changes that included amotivation and deviant social behaviors[33]. Similarly in humans damage to the dorsal ACC is associated with apathetic behaviour, lack of initiation, and movement execution[34]. In our findings, the areas in OFC (included BA 11, 47) and ACC (BA 24, 32) that correlated with PEM extended beyond the traditionally associated regions involved with reward and emotion regulation for OFC (BA 25 and 11) and ACC (BA 24). However, there is evidence that BA 47 in the OFC participates in drug and monetary rewards[35,36] and that BA 32 in the

dorsal ACC is involved in linking reward-related information with appropriate actions[37,38] and both BA 47 and BA 32 are implicated in addiction[36,39].

The investigation of the neurobiological processes underlying personality may help understand the mechanisms by which personality can serve as either a vulnerability factor or a protective factor in psychopathology[1]. For SUD the personality trait of positive emotionality has been associated with protection against these disorders. Thus, we surmise, based on our results that increased activity in OFC and ACC, could be linked with personality traits that offer a protection against SUD. Indeed, studies in substance abusers have consistently reported abnormal function of OFC and ACC[40,41]. Moreover, in subjects that despite a high genetic risk for alcoholism were not alcoholics the higher than normal striatal D2R receptor availability was associated with OFC (BA 11, 25, 47) and CG (BA 24, 32) metabolism, which led us to postulate that these prefrontal regions may mediate resilience of these subjects to alcoholism[6].

In contrast, certain personality traits of reward dependency, novelty seeking and impulsivity have been linked to a greater vulnerability for SUD[42]. Imaging studies on the neurobiology of novelty seeking traits in healthy controls (n=31) reported a negative correlation with metabolism in precuneus and BA 7 and a positive correlation between reward dependency and caudate metabolism[43]. The findings in precuneus and BA 7 showing a negative correlation with novelty seeking (trait that increases SUD risk), coupled with our findings showing of a positive correlation with PEM (personality dimension that is protective for SUD) implicates these regions as neurobiological substrates that may contribute to the vulnerability for SUD. A negative correlation between novelty seeking and metabolism in right middle temporal gyrus (as well as midbrain and parahippocampal gyrus) reported in a different study of healthy controls (n=16)[44] also follows an opposite pattern to the positive correlation we report between PEM and metabolism in middle temporal gyrus (BA 21). The precuneus, superior parietal lobe, and the middle temporal gyrus are not regions traditionally associated with rewards or SUD and therefore their potential role is unclear. On the other hand, these regions form part of the DMN that is associated with resting activity[26] (Figure 2 shows the overlap with DMN), which alerts about the potential importance of an hypoactive DMN in the vulnerability for SUD. Alternatively as discussed below increased activity of the DMN at rest may be a neurobiological substrate linked with the personality dimension of positive emotionality.

The unexpected positive correlation between PEM and metabolism in a broad array of cortical regions, was not observed for NEM or the Constraint dimensions. Since the metabolic measures were obtained at baseline (no

stimulation) this raises the possibility that the personality trait of PEM may relate to global cortical processes that are active during resting conditions (ie. introspection, mind wandering)[26]. Consistent with this interpretation is the pattern of correlations observed with the PEM that included regions implicated in the DMN (precuneus, BA 40, middle frontal cortex, middle temporal gyrus) and some more restricted overlap with regions implicated in the dorsal attention network (dorsal ACC, dorsolateral prefrontal cortex, and superior parietal cortex) as well as visual regions.

This finding is also interesting in that PEM accounted for a significant portion of the overall intersubject variability in whole brain metabolism ($r = 0.49$), the functional significance of which in not properly understood as it relates to healthy individuals. Our findings would suggest that baseline brain energetics may contribute to the personality trait of positive emotionality. Considering that positive emotionality is characterized by a higher propensity to engage in social interactions (social closeness and social potency) and in activities (achievement), studies that evaluate the relationship between brain glucose metabolism and sustainability of effort and engagement may help clarify the nature of this relationship.

In this report we did not see an association on the SPM analysis (after voxel or cluster correction) between brain glucose metabolism and the Negative Emotionality or the Constraint factors of the MPQ unless we lowered the threshold of significance ($p < 0.01$, uncorrected). The overall lack of an association between baseline brain metabolism and NEM and Constraint factors could reflect the fact that we measured baseline brain activity (intrinsic activity) whereas imaging studies, which measure activation responses (evoked activity) may be better suited to assess these two dimensions of personality.

Another limitation of this study is that correlations do not connote causal associations and thus we can not determine from our findings if the associations between resting cortical metabolism including that in OFC and ACC are causally linked with the personality trait of positive emotionality.

In conclusion, we have related individual differences on personality measure of positive emotionality to regional activity in a broad range of cortical regions that included the OFC and ACC. This corroborates our working hypothesis that activity in OFC and ACC would be associated with PEM. Inasmuch as dysfunction of the OFC and ACC are linked to SUD, these findings support a common neural basis for personality constructs that protect against SUD and their dysfunction in addiction. In addition, we uncovered an

unpredicted association between PEM and baseline metabolism in a broad range of cortical regions (including regions of the DMN) that implicates the activity of resting networks in personality dimension of positive emotionality.

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## Supplementary Material

**1**

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**2**

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**3**

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## Acknowledgments

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## Footnotes

Supplemental material. Enclosed are the results for the correlations between PEM and baseline brain glucose metabolism done separately for Study 1 and Study 2. The SPM results are shown in Supplemental Figure 1 and Table 1and the results for the ROI analysis are shown in Supplemental Table 2. We also enclose the SPM results on the correlations between brain glucose metabolism and Negative Emotionality (Supplemental Figure 2) and Constraint (Supplemental Figure 3) for the threshold of significance $p < 0.01$, uncorrected. None of the results were significant after correction for multiple comparisons.

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