Transcriptome changes in Dhcr7-knockout mouse - an in vivo model of Smith-Lemli-Opitz Syndrome

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Keywords: cholesterol, oxysterol, 7-DHC, Dhcr7, SLOS

Cholesterol is essential for proper brain development, neuronal differentiation, and synaptogenesis. It is a key component of cell membranes and helps control the fluidity and function of the membranes. Cholesterol is the immediate precursor for synthesis of steroid hormones and bile acids, and cholesterol influences activity in the sonic hedgehog pathway, an important signaling cascade for morphogenesis in the brain.

SLOS is a neurodevelopmental disorder produced by an inborn error of cholesterol metabolism. Known symptoms of SLOS include facial dysmorphology, learning difficulties ranging from mild to severe, and the majority of clinical SLOS cases usually present with a wide variety of autism symptoms. The underlying physiology of SLOS has been found to be linked to mutations in the enzyme 7-dehydrocholesterol reductase (DHCR7), which controls the expression of 7-dehydrocholesterol (7-DHC), the immediate precursor to cholesterol. Mutation of Dhcr7 can inactivate the enzyme to different degree, leading to the accumulation of 7-DHC and a wide variety in expression of severity of symptoms among SLOS patients. However, lack of cholesterol is less critical for SLOS pathophysiology than 7-DHC accumulation: the high reactivity of 7-DHC toward peroxidation leads to the synthesis of 7-DHC derived oxysterols, which are highly toxic.

Using the Dhcr7-deficient mouse model and PCR arrays we are uncovering the molecular deficits associated with cholesterol deficiency and 7-DHC derived neurotoxicity within the nervous system. Our studies of developing midbrain transcriptome in the mouse model of SLOS show that cholesterol deficiency leads to changes in the mRNAs encoding enzymes of lipid and cholesterol biosynthesis pathways. In addition, we found that the expression of many nuclear receptors is downregulated. These changes are likely present in patients with SLOS, and studies of the Dhcr7-KO mouse models will help us understand the role of cholesterol biosynthesis in neural development and brain connectivity.
Depression is one of the most common and burdensome disorders worldwide. The most widely prescribed antidepressants are serotonin (5-HT) selective reuptake inhibitors (SSRIs), believed to provide therapeutic benefit by antagonizing the 5-HT transporter (SERT) and elevating extracellular 5-HT levels. Significant, indirect evidence supports this conclusion, although multiple SSRIs have been found to interact with a sizable number of non-trivial targets at physiologically relevant concentrations. Several of these targets, when manipulated pharmacologically or genetically, can induce some of the same biochemical and behavioral effects associated with SSRI administration, raising the question whether all of the effects of SSRIs are 5-HT mediated. In order to separate the 5-HT/SERT dependent effects from the non-SERT effects of SSRI administration, we developed a transgenic mouse line that expresses a point mutation in the SERT SSRI binding site, converting an Ile at amino acid 172 to Met (SERT M172) (Thompson et al, PNAS 2011). The M172 substitution is benign with respect to SERT protein expression and 5-HT transport activity in vitro and in vivo, but confers a marked reduction in sensitivity (10-1000 fold) to many SERT antagonists. In our prior studies, where SERT M172 was expressed on a 129S6/S4 background, WT mice on the same background demonstrated either meager or anomalous responses to SSRIs in classical, acute tests of antidepressant action (tail suspension test and forced swim test). Although insensitivity was documented for citalopram and fluoxetine in biochemical, physiological, and behavioral assays, deeper analyses of SSRI action, particularly with chronic administration, required moving the M172 variant to a more favorable genetic background. After producing SERT M172 mice congenic on a C57BL/6J background, we repeated our initial characterization studies, validating prior observations that the variant supports normal synaptosomal 5-HT uptake kinetics but disrupts the ability of multiple SSRIs to inhibit 5-HT uptake. Moreover, these SERT M172 mice permitted a clear demonstration that SERT, and enhanced extracellular 5-HT, is essential for the immobility reducing behavioral actions of acute administration of citalopram and fluoxetine. Our ongoing studies aim to evaluate the requirement of SERT interactions for the effects of chronic antidepressant action, as assessed in behavioral, biochemical and stem cell analyses. Additionally, RNA profiling of SSRI-treated SERT M172 animals will provide an opportunity to elucidate gene and protein expression networks dependent and independent of SSRI-modulated 5-HT signaling.
Axonal HDAC1 is required for p75 mediated retrograde apoptotic signaling

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Keywords: Neurotrophin, Neuronal apoptosis, p75, HDAC

Axonal injury often results in neuronal apoptosis, suggesting that there exists a retrograde apoptotic signal which is transported from the distal axon to the cell body. Several studies have implicated the p75 neurotrophin receptor (p75NTR) as a mediator of such injury-induced cell death. Here, we have used the sympathetic neurons cultured in microfluidic chamber devices to investigate the mechanisms involved in this retrograde apoptotic signaling. BDNF addition to the distal axon compartment resulted in more than 50% neuronal apoptosis, detected in the cell bodies. This retrograde apoptotic signaling required p75NTR internalization and gamma-secretase mediated proteolysis, specifically in the distal axons. The cleavage of p75NTR releases the receptor associated factor NRIF, which then translocates to the nucleus. Interestingly, p75NTR-mediated retrograde apoptotic signaling required the histone deacetylase HDAC1. HDAC1 was constitutively localized not only in the nucleus of the neurons, but also in the axons. Inhibition of HDAC1 activity in the distal axons or knocking down the deacetylase prevented neuronal apoptosis in response to BDNF on the distal axons. In contrast, neuronal survival in response to NGF on the distal axons was not HDAC1 dependent, indicating that the deacetylase is required for retrograde apoptotic, but not survival signaling. Current efforts are focused on identifying the HDAC1 substrate in the axons and characterizing the p75NTR-mediated retrograde apoptotic signaling following peripheral nerve injury in vivo.
A Role for p75NTR in Oxidative Stress-induced Axonal Degeneration and Neuronal Death

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Keywords: neurotrophin, apoptosis, p75ntr, oxidative stress, degeneration

The p75 neurotrophin receptor (p75NTR) mediates the death of specific neuronal populations during development of the nervous system and in response to cellular injury. During such events, signaling by p75NTR occurs through regulated proteolytic cleavage of the receptor by the metalloprotease TNF-α converting enzyme (TACE) and by the γ-secretase complex. Despite various studies demonstrating this pro-apoptotic role for p75NTR in response to cellular injury, the mechanisms which couple these injuries to initiation of p75NTR signaling remain poorly understood. In the present study, we demonstrate that p75NTR signaling is activated by 4-hydroxy-2-nonenal (HNE), a lipid peroxidation product commonly generated by oxidative stress. While HNE promoted dose-dependent neuronal death of wildtype sympathetic neurons, neurons lacking p75NTR were significantly protected from HNE-induced cell death. Similarly, axonal degeneration in response to HNE was significantly attenuated in p75ntr-/- neurons. Treatment of sympathetic neurons with HNE stimulated cleavage of p75NTR, and co-application of the metalloprotease inhibitor TAPI-1 or the γ-secretase inhibitor DAPT prevented this proteolysis. Pharmacological blockade of p75NTR cleavage protected sympathetic neurons from HNE-induced cell death, suggesting that proteolysis of the receptor is required for HNE-induced apoptosis. Interestingly, our studies suggest that the apoptosis induced by HNE was not inhibited by an antibody to the extracellular domain of p75NTR, indicating that the apoptosis is ligand independent. Deletion of p75NTR in vivo also protected sympathetic neurons from neurite degeneration induced by the oxidative stress-promoting neurotoxin 6-OHDA. Analysis of sympathetic innervation of the spleen following 6-OHDA treatment of p75ntr-/- versus wild type mice suggests that the knockout mice are resistant to this oxidative injury. These results suggest that oxidative stress promotes proteolytic cleavage of p75NTR by TACE and γ-secretase, thus leading to neurite degeneration and neuronal cell death. Currently we are exploring the mechanisms by which oxidative stress induces p75NTR cleavage. This work will enhance our understanding of the contributions of p75NTR to neurodegenerative cascades induced by cellular injury or disease.
High-affinity choline transporter trafficking and role in vesicle pool sorting

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Keywords: Choline Transporter, Vesicle Pools, Trafficking,

The high affinity choline transporter (CHT) is a presynaptic membrane transporter whose action is the rate-limiting step in acetylcholine synthesis. Disruptions in cholinergic signaling can lead to an array of disorders from central nervous system cognitive dysfunctions to peripheral motor neuropathies. Interestingly, CHT is located mainly on a subset of synaptic vesicles and intracellular compartments even though it exerts its action at the plasma membrane. This phenomenon indicates a uniquely regulated system for this neurotransmitter transporter. Further examination of CHT led to the discovery of an endocytic motif within the C-terminal tail. This motif, when altered, shows increased distribution of the transporter on the plasma membrane by compromising its ability to endocytose. The endocytic motif points to critical regulatory signals within the C-terminal tail of the transporter. Together, the intracellular localization and regulatory motifs within the amino acid sequence of the transporter allow us to hypothesize that the trafficking of the transporter is important for its regulation and function and could potentially play a role in synaptic vesicle organization. Further work to elucidate other mechanisms of regulation in the C-terminal tail will be crucial to understand more fully the transporter's role in cholinergic signaling.
Swip-10/Mblac1: Identification of a Novel Regulator of Dopamine Signaling Linked to Glial Control of Extracellular Glutamate Homeostasis


Keywords: dopamine

Multiple brain disorders are associated with disrupted dopamine (DA) signaling including Parkinson's disease, schizophrenia and addiction. In C. elegans, an inability to clear synaptic DA results in swimming induced paralysis (Swip). In a screen for animals that display DA-dependent Swip, we identified two mutants, vt29 and vt33, that alter the coding sequence of an undescribed gene, F53B1.6, now named swip-10. Sequence analysis reveals the swip-10 mutations lie within a highly conserved metallobetalactamase domain. A swip-10 promoter:GFP fusion reporter reveals expression of the gene in C. elegans glial cells in vivo, consistent with findings of the ability to rescue Swip behavior through expression of wildtype swip-10 in nematode glial cells. These findings, along with our demonstration of elevated DA neuron excitability, suggest that swip-10 functions in glial cells to regulate excitation of DA neurons. Previously, beta-lactam antibiotics have been shown to regulate expression of mammalian glial glutamate transporters; together with the swip-10 findings, we hypothesize that swip-10 acts within a glial pathway that has the ability to control extracellular glutamate homeostasis. In support of this hypothesis, we found that mutation of multiple glutamate transporters generates DA-dependent Swip. Additionally, mutation of the glutamate receptors genes, glr-4, glr-6 and mgl-1, suppresses the paralysis phenotype of swip-10. Overexpression of Mblac1, the mouse ortholog of swip-10, in HEK cells results in reduced Na+-independent glutamate transport activity supported by the glutamate/cystine exchanger (XC-). Finally, overexpression of Mblac1 in astrocytes alters synaptic glutamate signaling between neurons in glial/neuronal co-cultures. Together, these studies point to novel mechanisms by which glia regulate synaptic and extra-synaptic glutamate. Current experiments seek to identify Swip-10/Mblac1 substrates using a metabolomics, LC/MS-MS and to determine whether the beta lactam ceftriaxone previously shown to alter CNS glutamate transport in vivo, acts via antagonism of Mblac1. Our studies may offer insights into how glutamate homeostasis may be altered to increase risk of neurological and neuropsychiatric disorders including diseases that feature disrupted DA signaling. Continued efforts in the analysis of human MBLAC1 may reveal a novel therapeutic target that could lead to better medications to treat such brain disorders

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The adaptor protein GULP promotes Jedi-1-mediated phagocytosis through a clathrin-dependent mechanism.

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Keywords: Jedi-1, engulfment, GULP, phagocytosis, satellite glial cell

During the development of the peripheral nervous system the large number of apoptotic neurons generated are phagocytosed by glial precursor cells. This clearance is mediated, in part, through the mammalian engulfment receptor Jedi-1; however the mechanisms by which Jedi-1 mediates phagocytosis are poorly understood. Here, we demonstrate that Jedi-1 associates with GULP, the mammalian homolog of CED-6, an adapter protein required for phagocytosis mediated by the nematode engulfment receptor CED-1. Silencing GULP or mutating the NPXY motif in Jedi-1, which was required for GULP binding, prevented Jedi-1-mediated phagocytosis. How GULP promotes engulfment is not known. Interestingly, we found that Jedi-1-induced phagocytosis required GULP binding to clathrin heavy chain (CHC). During engulfment CHC was tyrosine phosphorylated, which was required for Jedi-mediated engulfment. Both phospho-clathrin and actin accumulated around engulfed microspheres. Furthermore, knock down of CHC in HeLa cells prevented Jedi-1-mediated engulfment of microspheres and knock down in glial precursors prevented the engulfment of apoptotic neurons. Taken together, these results reveal that Jedi-1 signals through recruitment of GULP, which promotes phagocytosis through a noncanonical phosho-clathrin-dependent mechanism.
Dopamine signaling in C. elegans is regulated presynaptically by a highly conserved ortholog of the atypical MAP Kinase ERK7/8

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Keywords: Dopamine, C. elegans, Transporters

The neurotransmitter dopamine (DA) acts across phylogeny to modulate fundamental aspects of physiology and behavior, including movement, appetite, reward and attention. The model system Caenorhabditis elegans is a powerful platform for the discovery and manipulation of genes controlling synaptic function, including genes that control DA production, secretion, inactivation and response. We have observed a phenotype that occurs in late larval animals where loss of the DA transporter, DAT-1, results in animals that paralyze over a course of 10 minutes when placed in water, whereas wild-type animals swim at a relatively constant rate for up to an hour. "Swimming-induced paralysis", or Swip, can be reversed pharmacologically by treatment with reserpine, which prevents vesicular DA packaging and release, as well as by genetic ablation of the DA biosynthetic enzyme tyrosine hydroxylase (cat-2) or the D2-like DA receptor dop-3. Using the Swip phenotype, we have performed a forward genetics screen to identify mutants that exhibit dat-1 like paralysis that can be rescued by reserpine treatment as well as by mutation of genes supporting DA synthesis and response. One such mutant, vt32, was localized by SNP mapping and whole genome sequencing to an uncharacterized gene, here referred to as swip-13. We find that swip-13 mutations result in significantly reduced sensitivity to the neurotoxic dat-1 substrate 6-OHDA, supporting a role for swip-13 in sustaining DAT-1 protein expression, surface trafficking and/or activity. We observe that swip-13 mutants also possess reduced DA levels, suggesting that they may either fail to recycle DA as seen in DAT knockout mice, or that the mutation has more pleiotropic actions on DA synthesis, packaging or release. Importantly, DA neuron- specific, transgenic expression of the wild-type swip-13 gene restores normal swimming behavior of swip-13 mutants, establishing expression by DA neurons as the key site of SWIP-13 expression to modulate DA signaling. Fluorescently- tagged, functional swip-13 protein localizes to DA terminals, consistent with a presynaptic role for SWIP-13. SWIP-13 protein is highly conserved, likely representing the nematode homolog of the atypical MAP kinase ERK7/8. Overexpression of human ERK8 with hDAT in the neuroblastoma cell line SH-SY5Y results in increased DA uptake, suggesting that ERK8 regulates hDAT. Further efforts to uncover the mechanisms by which SWIP-13 and ERK7/8 modulate DA signaling may provide novel insights into disorders associated with perturbed DA signaling and their treatment.
Glucagon-like peptide-1 receptor activation reduces cocaine reward

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Keywords: glucagon-like peptide-1, addiction, drug reward, conditioned place preference, dopamine

Glucagon-like peptide-1 (GLP-1) is an incretin hormone and neuropeptide that regulates energy homeostasis and feeding behavior in part through stimulation of high affinity GLP-1 receptors (GLP-1R). GLP-1 and GLP-1Rs are expressed within the brain, including within brain reward circuitry. In fact, GLP-1R activation within the mesolimbic dopamine system reduces the hedonic components of food intake, and GLP-1R activators are successful treatments for diabetes mellitus. Given the overlap between food and drug reward circuitries, we tested the hypothesis that activation of the GLP-1R would diminish cocaine reward. A long-lasting specific GLP-1R agonist, exendin-4 (Ex-4), was administered in conjunction with cocaine in a test of conditioned place preference (CPP). As expected, cocaine alone induced a robust CPP effect. However, Ex-4 at all of the given doses significantly blunted the rewarding properties of cocaine. Importantly, Ex-4 alone did not produce an aversion, as these mice had no change in chamber preference over the course of the study. These effects were not due to alterations in locomotor activity. In preliminary studies, another GLP-1R agonist, liraglutide, did not alter the rewarding properties of cocaine, likely due to pharmacokinetic and/or pharmacodynamic differences between these compounds. It is not clear if Ex-4 diminishes the rewarding properties of other psychostimulants; testing of additional compounds is currently underway. There are no available specific antibodies against GLP-1R, so we have developed a fluorescent in situ hybridization assay that allows us to measure expression of GLP-1R mRNA. GLP-1R transcript can be detected in multiple components of reward circuitry, including the lateral septum and nucleus accumbens. Double-labeling strategies are defining the cellular phenotypes of these GLP-1R expressing neurons.

Our data thus indicate that activation of GLP-1Rs attenuates the rewarding properties of cocaine, indicating the presence of a GLP-1R-dependent mechanism of psychostimulant reward. This research also strengthens the assertion that food and drug dependence share common mechanisms and presents a novel target for the treatment of drug abuse.
Acetylcholine (ACh) participates in multiple biological processes ranging from cardiovascular and motor function to attention and addiction. Deviations from homeostatic cholinergic signaling have been implicated in heart disease, myasthenia, addiction, Attention-Deficit Hyperactivity Disorder and Alzheimer’s disease (AD). Potentiation of cholinergic signaling through the use of inhibitors of acetylcholinesterase (AChE), the main, FDA-approved, therapeutic strategy in AD, validates the cholinergic system as a therapeutic target. The presynaptic, high-affinity choline transporter (CHT), the rate-limiting determinant of ACh synthesis, represents a largely unexplored target for visualization and manipulation of synaptic cholinergic signaling. We have embarked on an effort to expand CHT pharmacology via high throughput screening (HTS) efforts. Using stably-transfected cells expressing a mutant CHT that exhibits reduced endocytic capacity, and a membrane potential-based fluorescent assay that capitalizes on CHT electrogenicity, we screened ~300,000 compounds, identifying more than 2,500 potential novel inhibitors. Hit compounds were triaged based on activity in non-transfected cells, activity in [3H]choline transport assays, and chemical features that could support CNS uptake and medicinal chemistry efforts. In this effort, we identified 36 compounds that belong to 5 structural classes, and that are currently driving diversification efforts to increase potency and selectivity. One compound, ML352, demonstrates low nanomolar potency, activity for CHT inhibition in an ex vivo nerve terminals preparation, a lack of interaction with a large number of receptors, ion channels and transporters, and a desirable DMPK profile. Kinetic profiling suggests that ML352 is a noncompetitive inhibitor of CHT, consistent with an allosteric mode of action. In parallel with these efforts, we have also screened for allosteric potentiators of CHT function, with hits from these studies currently under evaluation. Finally, our studies reveal molecules that are active in the primary membrane potential-based assay yet are inactive at CHT, suggesting possible modulation of transporter-dependent ion flux versus substrate translocation. Together, our efforts provide a path to new tools to visualize and/or manipulate cholinergic biology, with the goal of accelerating therapeutic development for disorders linked to perturbed ACh signaling.
Patchy distributions of myelin and VGLUT2 align with cytochrome oxidase blobs and interblobs in the superficial layers of primary visual cortex

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Keywords: cytochrome oxidase blobs, VGLUT2, myelin, primate, visual cortex

The purpose of this study was to determine whether the regions of cortex known as the cytochrome oxidase (CO) "blobs" in primary visual cortex (V1), a pattern of oval-shaped structures demarcated by the CO staining technique, could be revealed using Gallyas myelin and VGLUT2 immunolabeling techniques. Few studies have examined the distribution of cytochrome oxidase, myelin, and vesicular glutamate transporters (VGLUTs) in relation to one another within the primary visual cortex of primate species. The traditional Gallyas myelin stain is typically used to examine the architectonic features of cortical areas, yet it is still unconfirmed if the blob-like patches seen via this technique relate to the CO blobs in V1. Similarly immunostains for vesicular glutamate transporter 2 (VGLUT2) have identified regions of thalamic input in V1, but VGLUT2 labeling patterns have not been directly compared to the CO blob structures. The staining pattern of CO, myelin, and VGLUT2, was examined in cortical layer III of V1, using blood vessel alignment between adjacent sections cut tangentially to the cortical surface. The distribution of all three stains is not homogenous throughout layer III, as each stain appears as dense patches surrounded by continuous areas of poorly-stained tissue. However, aligned sections confirm that the patches outlined in both myelin and VGLUT2 stains align with CO blobs. Here, we put forth a detailed description of the evidence for the colocalization of CO blobs with VGLUT2 and myelin patches in V1, from which we can derive novel findings concerning the functional role of CO blobs in primate visual cortex.
Rare Opportunities for Progress in ADHD: Behavioral and Pharmacological Analysis of Knock-In Mice Expressing an ADHD-Associated Dopamine Transporter Gene Variant

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Keywords: ADHD, dopamine, knock-in

Attention deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed childhood neuropsychiatric disorder. Disrupted dopamine signaling is often implicated in ADHD's underlying pathology. Furthermore, the most common pharmacotherapies for ADHD exert their effects through the dopamine transporter (DAT). The A559V DAT coding variant was found in two brothers with combined type ADHD. In vitro studies reveal that this variant has abnormal dopamine efflux that is blocked with AMPH application. We proceeded to create a knock-in mouse carrying A559V DAT. Administration of AMPH in the A559V DAT mice and recordings in an open field demonstrate that the A559V mice have a blunted response to AMPH. Exploring if there are altered signaling pathways could provide potential mechanistic explanations for the behavioral phenotypes observed in ADHD. This knock-in A559V mouse provides the first construct valid model with which the role of disrupted dopamine signaling can be explored in the context of ADHD.
Low-dose ketamine induces rapid and long-lasting antidepressant effects in humans, and this effect has been replicated in rodent models of depression. The mechanisms of this antidepressant effect are not fully understood. Ketamine acts as a noncompetitive N-methyl D-aspartate receptor (NMDAR) antagonist, and studies have demonstrated that the ifenprodil derivative Ro 25-6981 (Ro), which inhibits GluN2B-containing NMDARs, is also capable of reducing depression-like behaviors in rodents. However, recent studies have shown that ifenprodil derivatives have a number of off-target effects at other sites critical for affective disorders, including the norepinephrine and serotonin transporters. Further, systemic administration of compounds such as ketamine and Ro does not allow determination of circuitry crucial for their actions. The GluN2B subunit is highly expressed in the bed nucleus of the stria terminalis (BNST), where it plays an important role in long-term potentiation (LTP). Given multiple studies implicating the BNST in negative affective disorders, we sought to explore the role of the GluN2B subunit within the BNST on affective behavior.

First, we demonstrated that systemic ketamine (3mg/kg) and Ro (5mg/kg) decrease latency to feed in the Novelty-Induced Hypophagia (NIH) behavioral paradigm in naive wild-type mice, as well as following acute restraint stress. Interestingly, we did not find significant effects of either drug in the elevated zero maze (EZM) or forced swim test (FST). We next utilized a combination of floxed GluN2B mice and stereotaxic delivery of lentiviral Cre-recombinase to knock down the grin2b gene specifically from the BNST (BNSTGluN2BKO). Similar to ketamine- and Ro-treated wild type mice, BNSTGluN2BKO mice have significantly reduced latency to feed in the NIH paradigm but do not show alterations in the EZM or the FST. This effect was specific to GluN2B, as no effect was observed with similar LV-CRE injections into the BNST of floxed glucocorticoid receptor mice (BNSTGRKD). To determine the effects of BNST GluN2B deletion or systemic ketamine administration on plasticity within the BNST, we examined field potential induction of LTP in the BNST. We found that in BNSTGluN2BKO mice, an early component of LTP was enhanced compared to control virus (lentiviral GFP) injected mice. Systemic ketamine treatment blunted LTP, and did not rescue LTP following restraint stress. In total, these data suggest that GluN2B containing NMDARs in the BNST play an important role in modulation of affective behavior.
Dopamine (DA) signaling modulates the development of normal brain structure and function and is implicated in the pathophysiology of psychiatric diseases including schizophrenia. The striatum and medial frontal cortex receive significant dopaminergic innervations even prior to synaptogenesis, express high levels of dopamine receptors, and appear to be involved in the developmental origins of psychiatric disease. DA receptor activation alters dendritic trajectories in vivo, and neurite outgrowth in vitro. This regulation depends both on the brain region and receptor subtype activated, suggesting complex neuronal heterogeneity in responses. Our preliminary data confirms that modulation of the DA D1 receptor alters neurite outgrowth in both the striatum and medial frontal cortex. Whether the effects of D1 receptor (D1R) activation are cell autonomous is unknown. In addition, D1R activation can lead to activation of the neurotrophin receptor TrkB, which also has effects on neurite outgrowth. We hypothesize that D1R stimulation affects neurite outgrowth only in a D1R expressing subpopulation and that these effects are at least partially dependent on TrkB receptor signaling. We will culture dissociated striatal and cortical neurons from mice in which D1R expressing cells are labeled with tdTomato protein for identification. Colocalization studies with these mice have shown that tdTomato is stably expressed and localizes as expected with specific nuclear, signaling, and Ca++ binding protein markers. Neurite outgrowth effects will be measured following agonists and antagonists of D1Rs and in DA receptor knockout mice. Future studies with assess a causal link between D1R and TrkB signaling by testing whether D1R agonist effects are blocked by TrkB inhibition. We will also investigate whether D1R blockade modulates TrkB receptor-induced changes in morphology. We expect these results to support an autonomous effect of D1R stimulation on neurite outgrowth. We also expect that the effects of D1R agonists on neurite outgrowth will be partially or completely blocked by blocking TrkB-induced responses. Our studies will define a mechanism through which D1Rs alter neurite outgrowth in a cell-specific manner and may contribute to the development of psychiatric disorders.
What’s Serotonin Got to Do With It? Studies on the Actions of SSRIs and Cocaine in SERT M172 Mice

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Keywords: serotonin, cocaine, addiction

Decades of research indicates that DA reuptake blockade is primary for the neuroplasticities that lead to cocaine addiction. However, cocaine is well known to inhibit the serotonin (5-HT), dopamine (DA), and norepinephrine transporters at relatively equivalent potencies. To elucidate the role of 5-HT in cocaine action, we have developed and implemented a novel knock-in (KI) mouse model wherein the Slc6a4 gene has been mutated to eliminate high-affinity binding of cocaine to the 5-HT transporter (SERT Met172). Unlike SERT KO mice, these animals express normal levels of SERT and normal 5-HT transport, precluding compensatory changes that normally attend constitutive loss of signaling molecules. Using synaptosomal preparations, we assessed the loss of high-affinity recognition of cocaine and the cocaine analog RTI-55 in the KI model ex vivo vs WT littermates. For these agents, we observed an 80- and 650-fold reduction in potency for 5-HT uptake inhibition, respectively. In contrast, no change was seen in the inhibitory potency of amphetamine and 3,4-methylenedioxymethamphetamine (MDMA), agents that, like 5-HT, do not interact with the Met172 substitution. To assess the 5-HT contribution to cocaine-induced behavioral plasticities, we measured the preferences of KI vs WT animals for cocaine in the 2-bottle choice paradigm. We found that KI mice exhibited a reduced preference for cocaine in the first week of administration relative to WT animals. However, by week two, the KI animals demonstrated an exaggerated preference for cocaine vs WT littermates. These finding reveal a significant, timedependent, suppressive role of SERT antagonism, in the drive of mice to continue to consume cocaine. Our studies are now being extended to other behavioral paradigms used to study cocaine action, as well as to an evaluation of molecular changes that derive selectively from SERT antagonism by cocaine.
Vitamin C (ascorbic acid) is an essential micronutrient and antioxidant. It is found in higher concentrations in the brain than in any other organ, and the concentration is even higher during early development. In in vitro experiments vitamin C is critical for differentiation of neurons from pluripotent stem cells. We therefore, chose to investigate the role of vitamin C in neurogenesis. Initial experiments were conducted in adult mice. The mice used expressed either decreased (SVCT2+/-) or increased (SVCT2-Tg) levels of the specific transporter required for transport of vitamin C into the brain (SVCT2) and showed either a 30% decrease or up to 150% increase in brain vitamin C, respectively. These mice were compared to wild-type mice with normal transporter expression and vitamin C level. The hypothesis tested was that low vitamin C would lead to decreased neurogenesis. All mice were male, and were tested at 4-5 months of age. Mice were treated with BrDu (50 mg/kg, IP) for 7 days prior to sacrifice. Immunohistochemical study of hippocampal regions was used to identify and count the number of new, BrDu-positive, neurons in multiple sections per mouse. Future studies will be extended to examining the role of neurogenesis during prenatal development under different levels of vitamin C deficiency.
Drosophila MMPs Regulate Trans-Synaptic Signaling, Synaptic Architecture and Neurotransmission Strength

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Keywords: Drosophila, neuromuscular junction, synaptogenesis, matrix metalloproteinase, extracellular matrix

Matrix metalloproteinases (MMPs) are a conserved family of secreted and membrane-tethered zinc-dependent extracellular proteases that act on secreted signaling ligands, membrane receptors and extracellular matrix (ECM) proteins in many diverse processes ranging from development to immune response. In mice, 24 MMPs are regulated by 4 tissue inhibitors of MMPs (TIMPs), whereas Drosophila has only 2 MMPs (secreted MMP1 and GPI-anchored MMP2) and a single TIMP, making it very attractive for genetic dissection. Our studies suggest that MMPs play key roles in the Drosophila nervous system, including synaptogenesis at the neuromuscular junction (NMJ). Bidirectional trans-synaptic signaling between motoneuron and muscle requires ligands to move across a specialized extracellular environment (the synaptomatrix) hypothesized to be modulated by MMP activity. MMPs localize to the synaptomatrix and MMP dysfunction is associated with neurological disorders such as Fragile X syndrome (FXS), which manifests synaptogenesis defects as the most common heritable form of autism spectrum and intellectual disability disorders. Recent studies in both mouse and Drosophila FXS models implicate MMP dysfunction as an underlying cause of FXS phenotypes. Synaptogenesis defects caused by loss of the Fragile X Mental Retardation Protein (FMRP) are alleviated by pharmacological MMP inhibition, TIMP overexpression and MMP co-removal. However, little is known about MMP functions at the synapse or the intersection of FMRP/MMP requirements. Preliminary data show that MMP1/2 negatively regulate NMJ structure and function, modulating Heparan Sulfate Proteoglycans (HSPGs) and trans-synaptic signaling pathways also known to be misregulated in the Drosophila FXS model. I therefore hypothesize that MMP proteolytic activity, balanced by TIMP inhibition, regulates synaptomatrix composition to modulate trans-synaptic signaling that coordinates structural and functional NMJ synaptogenesis, and that this activity intersects with the role of FMRP in a mechanism causative for the Fragile X syndrome disease state.
Conditional Elimination of the Interleukin-1 Receptor for the Study of the Impact of Inflammatory Cytokines on Brain and Behavior

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Keywords: serotonin, immune system, serotonin transporter, interleukin-1 receptor

The presynaptic 5-HT transporter (SERT) limits access of 5-HT receptors to the neurotransmitter in the brain and periphery and is a target for widely prescribed antidepressant medications. We have shown (Zhu et al. 2006; Chang et al. 2012) SERT to be regulated by a p38 MAPK linked pathway downstream of IL-1 receptor (IL-1R) activation by IL-1β. Since IL-1Rs are expressed throughout the body, including the CNS, constitutive IL-1R KO mice are insufficient to determine the site(s) and timing of receptor expression and IL-1β that support 5-HT dependent behavioral changes. To pursue this question, we have generated mice suitable for the conditional elimination of the IL-1R (IL-1Rflox/flox). We used a conventional homologous recombination approach to insert loxP sites flanking the 3rd and 4th exons of the Il1r1 gene in 129S6 embryonic stem cells. IL-1Rflox/flox animals have been produced that are congenic on a 129S6 background and approaching congenic status on a C57BL/6J background. Initial characterization of IL-1Rflox/flox mice reveals that these animals are viable, reproduce normally, and display no gross abnormalities. To determine whether the presence of loxP sites is detrimental to IL-1R gene expression, we used quantitative RT-PCR to determine relative IL-1R mRNA expression in both midbrain and spleen of 129S6 IL-1Rflox/flox mice and wild type (WT) 129S6 controls. These studies revealed no alterations of IL-1R mRNA levels in either midbrain or spleen, consistent with the benign nature of inserted loxP sites. Additionally, IL-1Rflox/flox animals demonstrate normal paroxetinesensitive, synaptosomal SERT activity. Intact IL-1R mRNA expression and SERT activity provides an optimum background for evaluation of the actions of the cytokine receptor in vivo. The availability of these mice will allow for the regional and temporal elimination of IL-1Rs, providing a powerful tool to dissect the actions of IL-1β in the brain and periphery. Successful, raphe-specific, p38 MAPKα elimination has been achieved using ePET-1 Cre mice (Scott et al. 2005) and efforts are now being pursued to use the same approach to eliminate the IL-1R in 5-HT neurons. With respect to our goals, these animals will afford a critical opportunity to evaluate IL-1R-mediated p38 MAPK signaling in the activation of SERT at synapses and the role of this activation in 5-HT signaling and behavior. Given the comorbidity of immune system dysfunction with multiple neuropsychiatric disorders, our animal model should have translational relevance, including the examination of immune system-based therapeutics.
Stuck on SERT: Do Changes in Serotonin Transporter Protein Associations Impact Risk for Autism?

Meagan A Quinlan, Ran Ye PhD, Matthew Robson PhD, Hideki Iwamoto PhD, Jeremy Veenstra-VanderWeele MD, Randy Blakely PhD

Keywords: Serotonin Transporter, Autism

Autism spectrum disorder (ASD) is characterized by deficits in three core domains: social interactions, language and communication, and behavioral flexibility. Accumulating evidence suggests that perturbed serotonin (5-HT) signaling may play a role in ASD susceptibility. A major regulator of 5-HT signaling is the presynaptic 5-HT transporter (SERT, SLC6A4) that terminates 5-HT actions at synapses by rapidly clearing the neurotransmitter after release. Our lab has identified five coding variants in SERT subjects with autism, each of which confers constitutively increased 5-HT transport capacity. The most common of these variants (~1% of the U.S. population) is a substitution of Gly for Ala at amino acid 56 (SERT Ala56). This gain-of-function SERT mutation also shows a loss of PKG/p38 MAPK mediated up-regulation, a p38 MAPK dependent hyper-phosphorylation and an enhanced sensitivity to PKC regulated 5-HT uptake. Currently, the molecular mechanisms driving elevated activity of SERT Ala56 and its disrupted regulation are unknown. To elucidate physiologically significant consequences of SERT Ala56 in vivo, our lab developed a knock-in mouse model, expressing SERT Ala56 from the endogenous Slc6a4 locus. Using this model, I will test the hypothesis that both elevated transport function and altered regulation derive from modified protein associations including interactions the transporter's N-terminus where the Ala56 substitution occurs. I will also determine whether modified associations are driven by transporter phosphorylation and if so what kinase/phosphatase pathways are involved. Finally, I will determine how the SERT Ala56 variant contributes to functional alterations in 5-HT signaling and how these changes may be reversed by a better understanding of protein associations and/or transporter phosphorylation. Together, these efforts will elucidate mechanisms by which perturbed 5-HT inactivation can contribute to risk for ASD as well as other disorders, such as depression, linked to alterations in CNS 5-HT homeostasis.
Stress and noradrenergic modulation of extended amygdala projecting dopamine neurons of the rostral linear nucleus

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Keywords: dopamine, stress, norepinephrine, addiction, BNST

Stress can induce pathological conditions such as anxiety disorders, post-traumatic stress disorder (PTSD), and drug abuse. Dopamine signaling in the bed nucleus of the stria terminalis (BNST) and central nucleus of the amygdala (CeA), regions of the extended amygdala, may be important for stress- and addiction-related behaviors. Anatomical studies in rats indicate that a large portion of the dopamine input to the extended amygdala arises from midline dopamine neurons located in the ventral lateral periaqueductal gray (vlPAG) and the rostral and caudal linear nuclei of the raphe (RLi and CLI). These midline dopamine neurons remain largely unstudied regarding stress, anxiety, and addiction related behaviors. However, there is evidence that these cells play a key role in opiate reward behaviors and are activated during stress. These midline dopamine neurons receive substantial norepinephrine (NE) input from the locus coeruleus and other brainstem norepinephrine centers. We hypothesized that stress recruits the RLi dopamine neurons via noradrenergic signaling. We found that immediate early gene zif268 immunoreactivity increases in tyrosine hydroxylase (TH) positive cells of the mouse RLi after 60 minutes of restraint stress, indicating that stress activates a subset of midline dopamine neurons. Whole cell electrophysiology recordings in the RLi from a TH-eGFP BAC transgenic reporter mouse indicate that norepinephrine application increases the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) in RLi dopamine neurons. This effect on glutamatergic transmission is mediated through the α1 adrenergic receptor (AR), as the actions of norepinephrine are mimicked by the α1-AR selective agonist methoxamine and blocked by the α1-AR selective antagonist prazosin. The actions of the agonist on sEPSCs appear to be transient as it did not persist in the presence of prazosin. Methoxamine also increases the frequency but not amplitude of miniature EPSCs, further indicating that the α1-AR action on glutamatergic transmission has a presynaptic mechanism. The application of norepinephrine in the presence of the α1-AR antagonist prazosin leads to a decrease in the frequency of sEPSCs that is most likely mediated by the α2-AR. The overall effect of norepinephrine on the firing of RLi dopamine neurons is currently being examined. These studies provide early insight into the importance of the role of extended amygdala projecting dopamine neurons in the stress response.
Depression is the primary cause of disability worldwide and has long been linked to alterations in serotonin (5-HT) signaling, as well as perturbed immune system function. We are pursuing the hypothesis that depression may represent an inappropriate expression of basic physiological processes normally organized to modulate behavior in the context of immune system activation. Supporting this concept, patients diagnosed with depression often display higher levels of proinflammatory cytokines, such as interleukin-1β (IL-1β). Moreover, peripheral administration of IL-1β and other inflammatory agents produces depressive-like effects on behavior in rodents and humans, effects that can be attenuated or eliminated with antidepressant medications. Despite these long-standing observations, the cellular and molecular pathways by which immune system activation alters behavior remain ill defined. We propose that one of these pathways involves immune system signaling to, and through, regulatory pathways that insure proper 5-HT signaling. A prominent control point for 5HT signaling is the presynaptic, antidepressant-sensitive 5HT transporter (SERT, SLC64A). SERT activity can be rapidly increased by IL-1 receptor (IL-1R) activation in vitro by IL-1β through a p38 MAPK-dependent pathway. Additionally, i.p. injection of lipopolysaccharide (LPS) rapidly enhances synaptosomal 5-HT transport and 5-HT clearance. Finally, LPS also produces a depressive-like effect on behavior as assessed in the tail suspension (TST) and forced swim tests (FST), effects that are absent in IL-1R KO mice. Since early-life stress is a risk factor for the development of mood disorders in adults, and in animal models produces changes in adult immune system activation, we have implemented a maternal separation (MS) model to investigate whether the ensuing anxiety and depressive behavior of adult animals is dependent on IL-1R function and also whether such signaling involves early or later life (or both) modulation of CNS 5-HT signaling. Here we provide evidence that the anxiety- and depressive-like effects of MS observed in older animals are lost in IL-1R KO mice. Ongoing studies with conditional, raphe-specific elimination of IL-1R and p38 MAPK seek to determine whether CNS 5-HT neurons provide a critical link between early life stress, the immune system and risk for depression.
Genetic Variation in Melatonin Pathway Enzymes in Individuals with Autism Spectrum Disorder and Comorbid Sleep Disorders

Olivia J. Veatch, Julie S. Pendergast, Melissa J. Allen, Carl H. Johnson, and Beth A. Malow

Keywords: Genetics, Autism Spectrum Disorder, Sleep Disorders, Candidate genes, Pharmacogenetics

Previous studies established a strong influence of common genetic variation in the etiology of autism spectrum disorder (ASD). However, there are major challenges identifying even modest, replicable effects related to this variation. It is possible that variable phenotypic expressivity can be explained by underlying genetic differences. A large proportion of individuals with ASD present with comorbid sleep disorders. Disrupted sleep not only affects cognitive functioning, but exacerbates ASD-related behavioral impairments. It is understood that genetic factors regulate the sleep-wake cycle in humans. Stratifying ASD cases based on presentation of sleep disruption may help address issues related to phenotypic heterogeneity in genetic analyses.

Our hypothesis was that individuals with ASD and comorbid sleep onset delay, that respond to supplemental melatonin, will harbor a greater load of variation in genes related to maintenance of endogenous melatonin levels than individuals with no evidence of sleep disorders, or where melatonin supplementation is shown ineffective.

We sequenced the protein coding region of the Acetylserotonin O-methyltransferase (ASMT) gene in a group of patients diagnosed with ASD and comorbid sleep onset delay. All patients had positive responses to treatment with supplemental melatonin. We also genotyped seven single nucleotide polymorphisms (SNPs), in the cytochrome P450 1A2 (CYP1A2) gene, that are reported to affect metabolic activity of this enzyme.

We observed seven commonly occurring SNPs in ASMT. All patients were either homozygous or heterozygous for functional variants previously associated with ASD risk. Compared to current estimates in ASD without reported evidence of sleep disturbances we observed similar, and in some cases, higher allele frequencies for SNPs suspected to alter ASMT transcript production. Six of the seven SNPs genotyped in CYP1A2 were polymorphic in our patients. We observed higher polymorphism rates compared to current reports for ASD patients diagnosed as slow melatonin metabolizers. Melatonin supplementation for these patients was also shown to exhibit disappearing effectiveness over time. This phenomenon was not observed for the patients we evaluated. We also observed substantially higher frequencies for variant alleles related to decreases in CYP1A2 enzymatic activity than currently reported for populations of European ancestry.

We found that individuals with ASD and comorbid sleep onset delay, responsive to supplemental melatonin, harbored a greater load of genetic variation, especially in CYP1A2, compared to current reports. This supports the hypothesis that, in individuals with ASD, sleep onset delay and treatment response is related to variation in melatonin pathway genes.
Poster: 23 Session: 1

Presenter: Patricia Jumbo-Lucioni (patricia.jumbo@vanderbilt.edu) Lab PI: Kendal S Broadie

Altered Glycosylated Synaptomatrix Composition and Synaptic Architecture in a Drosophila Classic Galactosemia Disease Model

Patricia P. Jumbo-Lucioni, Kendal S Broadie

Keywords: glycosylation, galactosemia, synaptomatrix, neuromuscular junction

Classic galactosemia (CG) is an autosomal recessive disorder that results from loss of galactose-1-phosphate uridylytransferase (GALT), the Leloir pathway enzyme which catalyzes conversion of galactose 1-phosphate + UDP-glucose to glucose 1-phosphate + UDP-galactose. UDP-galactose 4'-epimerase interconverts UDP-galactose to UDP-glucose, and is responsible for the biosynthesis of UDP-N-acetylgalactosamine and UDP-N-acetylglucosamine. All four UDP-sugars are essential donors for the synthesis of glycoproteins and glycolipids that heavily decorate cell surfaces and the extracellular space. In addition to acute, potentially lethal neonatal symptoms in CG, mature patients develop substantial motor and cognitive impairments. Previous studies suggest an association of neurological phenotypes and glycosylation defects, with CG described as a Congenital Disorder of Glycosylation (CDG) with a combined defect in the assembly and processing of N-glycans. Based on this prediction, our goal has been to test for impacts on behavioral traits, synaptic development and glycosylated synaptomatrix formation using a GALT-deficient Drosophila CG model. We tested larval coordinated movement, adult locomotion and daily activity levels, and found that loss of dGALT impairs all three traits. We characterized larval neuromuscular junction (NMJ) structure, and found that GALT-deficient larvae exhibit structural overelaboration with increased bouton and branch number, increased process length and decreased bouton diameter and inter-bouton distance. Dietary galactose supplementation and coremoval of the dGALK gene establish environmental and genetic modifiers of these behavioral and neurological phenotypes. We assayed the extracellular synaptomatrix with a panel of lectin labels and found profound alterations in the glycan composition in the absence of dGALT, including significant reductions in the amount of galactosyl and N-acetyl galactosamine residues, and fucosylated HRP epitopes. Synaptogenesis is driven by bidirectional trans-synaptic signals modulated by the synaptomatrix carbohydrate environment, and dGALT mutants display striking changes in the expression of heparan sulfate proteoglycan (HSPG) co-receptor as well as Wnt ligand levels. Taken together, these results reveal synaptic glycosylation defects downstream of UDP-gal deficiency, synaptic architecture defects, and concomitant changes in synaptogenesis signaling pathways, and raise the intriguing possibility that pharmaceutical inhibition of GALK might benefit the CG disease state. Similar mechanistic defects during synaptogenesis may account for the neurological pathogenesis characterizing a wide array of CDGs.

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Poster: 24 Session: 2

Presenter: Peter Hamilton (peter.j.hamilton@vanderbilt.edu) Lab PI: Aurelio Galli

Phosphatidylinositol (4,5)-bisphosphate regulates psychostimulant behaviors through its interaction with the dopamine transporter

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Keywords: dopamine transporter, phosphatidylinositol 4,5-bisphosphate, Drosophila melanogaster, amphetamine,

Phosphatidylinositol (4,5)-bisphosphate (PIP2) is known to regulate the function of ion channels and transporters. The human dopamine (DA) transporter (hDAT) is a key regulator of DA homeostasis and a target of the psychostimulant amphetamine (AMPH). AMPH’s addictive properties are mediated, at least in part, through elevation of extracellular DA by inducing DA efflux through the DAT. Thus, the objective of our study is to understand how to precisely manipulate the DAT to prevent DA efflux without altering its physiological function of DA uptake. This understanding is paramount to the development of pharmacological therapies for AMPH abuse. Here, we demonstrate that PIP2 directly binds to the hDAT. This binding occurs through electrostatic interactions with positively charged hDAT N-terminal residues and is shown to facilitate AMPH-induced, DAT-mediated DA efflux and the psychomotor properties of AMPH. Substitution of these residues with uncharged amino acids reduces hDAT-PIP2 interactions and AMPH-induced DA efflux, without altering the hDAT physiological function of DA uptake. We evaluated, for the first time, the significance of this interaction in vivo using locomotion as a behavioral assay in Drosophila melanogaster. Expression of mutated hDAT with reduced PIP2 interaction in Drosophila DA neurons impairs AMPH-induced locomotion without altering basal locomotion. We present the first demonstration of how PIP2 interactions with a membrane protein can regulate organismal behaviors, such as locomotion.
Sink or Swim: Identifying novel regulators of presynaptic dopamine signaling

Sarah Baas Robinson, J. Andrew Hardaway, Shannon Hardie, Sarah Whitaker, Tessa Popay, Phyllis Freeman, Randy Blakely

Keywords: dopamine transporter, C. elegans

Dopamine (DA) modulates brain circuitry relevant to cognition, reward, motor control, and arousal. Perturbed DA signaling is believed to contribute to addiction, ADHD, schizophrenia, and Parkinson’s disease. The presynaptic DA transporter (DAT) is a major control point for DA signaling and increasing evidence indicates that altered regulation of DAT may contribute to risk for these disorders. We have chosen the nematode Caenorhabditis elegans as a model system to elucidate novel mechanisms regulating DAT and/or DA signaling. We have demonstrated that DA is important for swimming behavior in the worm, as ablation of the C. elegans gene encoding DAT (dat-1) results in swimming-induced paralysis (Swip). This behavior is attenuated in animals treated with the vesicular monoamine transporter inhibitor, reserpine, and is dependent on signaling through a postsynaptic, D2-like receptor, DOP-3. To determine novel presynaptic regulators of DA signaling, we undertook a chemical mutagenesis screen to identify reserpine-sensitive Swip animals. Two mutants, vt31 and vt34, do not possess mutations in dat-1, fail to complement and map to the same region on LG1. Similar to dat-1 null animals, these mutants exhibit robust Swip that is suppressed by deletions in cat-2 or dop-3. Overexpression of GFP::DAT-1 does not rescue Swip in these mutants, despite normal trafficking of the protein to the synapse. The mutants are partially resistant to the toxin 6-hydroxydopamine, which requires uptake by DAT-1 to produce DA neuron degeneration, consistent with reduced DAT-1 function. Unlike dat-1 animals, vt31 and vt34 have altered male tail morphology, which we found arises from a premature stop codon in the Runx transcription factor homolog RNT-1. Ongoing experiments will determine whether the rnt-1 mutation underlies the Swip phenotype in these mutants. Elucidation of the molecular lesion associated with vt31 and vt34 may yield important and conserved clues to the presynaptic regulation of DA signaling. Supported by NIH awards MH095044 to RDB, T32 MH065215 (S.B.), F31 MH093102 (A.H.), and MH095044 (R.D.B).
Abnormal Dopamine Signaling and Response to Amphetamine in Mice Expressing an ADHD-associated Dopamine Transporter Coding Variant

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Keywords: Dopamine Transporter, ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is a widespread developmental neuropsychiatric disorder characterized by hyperactivity/impulsivity and inattention likely caused by the dysfunction in dopamine (DA) signaling pathways. The presynaptic dopamine transporter (DAT) is the target for the most common pharmacological therapies for ADHD (amphetamine and methylphenidate) and is responsible for terminating DA signaling via reuptake of DA into the presynaptic terminal. Previous work in the lab provided first evidence for a heritable, functional ADHD-associated Ala559Val (A559V) DAT coding variant isolated from two subjects diagnosed with ADHD and showed that cells expressing A559V-DAT exhibit anomalous basal outward DA leak (efflux) that was blocked by amphetamine (AMPH), while AMPH typically induces DA efflux in cells expressing the WT-DAT. Owing to the striking phenotype of A559V DAT in vitro, and the lack of ADHD mouse models with good construct validity, studies in the lab have since focused on the generation and subsequent characterization of a knock-in mouse model expressing A559V DAT. After initial in vivo characterization of mice expressing A559V DAT, we observed that while there is no change in basal locomotor activity, there is a blunted locomotor response upon treatment with AMPH. Interestingly, we observed decreased [3H] DA release after AMPH treatment from striatal slices and decreased vesicular [3H] DA release upon K+ stimulation. We also demonstrated a decrease in endogenous DA release in response to amphetamine by in vivo microdialysis. Furthermore, we also showed using whole-cell patch-clamp electrophysiology experiments that DA neurons in VTA slices of A559V DAT knock-in mice exhibit decreased resting membrane potentials and reduced firing rates. Although the A559V DAT variant is rare, these initial findings highlight the validity of the A559V DAT mice as a first, valuable model for ADHD and underscore the importance of altered DA signaling and DAT dysfunction as risk factors in ADHD. Future work will focus on further biochemical and physiological in vivo characterization of the A559V DAT looking at putative alterations in DAT regulation.
A Novel Trans-synaptic Neuroligin 2/Serotonin Transporter Protein Complex Regulates Serotonin Signaling

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Keywords: serotonin, neuroligin 2, autism, ,

Compromised serotonin (5-HT, 5-hydroxytryptamine) signaling has been implicated in multiple neuropsychiatric and neurodevelopmental disorders including depression, obsessive-compulsive disorder (OCD), anxiety and autism. The presynaptic 5-HT transporter (SERT) is the primary mechanism of extracellular 5-HT inactivation and is a major target of antidepressant medications. In an effort to identify novel regulators of 5-HT signaling, we implemented proteomic and genetic paradigms, efforts that converged on the synaptic cell adhesion gene neuroligin 2 (Nlgn2). Whereas NLGN2 protein appears to coordinate GABA signaling in the forebrain, our profiling of midbrain RNA expression in recombinant inbred mice revealed that Nlgn2 gene expression strongly correlated with the expression of multiple genes required for 5-HT identity and signaling, including Fev (PET-1), Tph2, and Slc6a4 (SERT). These results converged with proteomic and co-immunoprecipitation studies which showed that NLGN2 forms stable, midbrain-specific protein associations with SERT. These findings have led us to hypothesize that NLGN2 makes critical contributions to both 5-HT and GABA mediated regulation of raphe neurons via a somato-dendritic SERT/5-HT1A/NLGN2/GABAA receptor complex. Our preliminary data using constitutive NLGN2 KO mice demonstrate that NLGN2 is required to maintain normal 5-HT levels, normal SERT protein expression, and performance on tasks sensitive to antidepressants. NLGN2 KO mice also displayed social avoidance as they backed away more frequently when confronted by another mouse in tube test. Our findings on the essential roles of NLGN2 in 5-HT signaling may relate to the rare gene variants in NLGN2 identified from subjects with neuropsychiatric disorders and raises the possibility that psychiatric disorders traditionally associated with altered 5-HT signaling may in some cases originate from perturbation of cell-adhesion mechanisms linking 5-HT and GABA signaling in the midbrain.

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Functional modulation of secretion by Ca2+-Dependent Activator Protein for Secretion (CAPS1) RNA editing

Randi J. Ulbricht, Roman Lazarenko, Qi Zhang and Ronald B. Emeson

Keywords: RNA, secretion, exocytosis

Adenosine-to-ino sine (A-to-I) RNA editing is a post-transcriptional modification by which adenosine residue(s) are selectively deaminated by Adenosine Deaminase Acting on RNA (ADAR) enzymes. The base-pairing qualities of inosine allow it to be read as guanosine during translation, oftentimes altering the coding potential of mRNA. A recent genome-wide study revealed that a single adenosine nucleoside within RNA transcripts encoding the C-terminal domain of human Ca2+-dependent activator protein for secretion (CAPS1) is subject to an RNA editing event, converting a glutamate (GAG) to a glycine (GIG) codon. CAPS1 is one of two CAPS homologs that promote the storage and release of hormones, neuropeptides and monoamine neurotransmitters.

Our studies focus on defining the role of RNA editing in regulating CAPS1-mediated release. We first analyzed RNA from several species to determine that RNA editing-mediated changes to CAPS1 coding potential are conserved in vertebrate nervous systems. Next, we quantitatively analyzed CAPS1 editing from mouse to reveal differential levels of editing in peripheral endocrine tissues and selected brain regions. We then determined the editing potential of various CAPS1 minigene constructs expressed in heterologous cell culture systems, defining the mammalian enzyme that catalyzes CAPS1 editing and the cis-elements that are required for ADAR recognition. Importantly, our work to define the functional implications of CAPS1 editing suggests that neurotransmission is differentially affected by the expression of edited or non-edited CAPS1 both pre- and post-synaptically.

This work provides the first detailed analysis of CAPS1 editing patterns across species and tissues, defines the molecular mechanism underlying this RNA processing event, and indicates its evolutionary significance. Most importantly, these studies provide critical insights into the critical role that RNA editing plays in the modulation of CAPS1-dependent exocytosis and how dysfunction of this process may contribute to disorders where alterations in hormone/neurotransmitter release have been implicated.
In Vivo Analysis of Sequences Required for Synaptic Localization of the Presynaptic Dopamine Transporter

Sarah Baas Robinson, Andrew Hardaway, Ryan Glynn, Shannon Hardie, Randy D. Blakely

Keywords: dopamine transporter, C. elegans

The monoamine neurotransmitter dopamine (DA) modulates brain circuitry relevant to cognition, reward, motor control, and arousal. Defects in DA signaling have been implicated in risk for addiction, attention-deficit hyperactivity disorder (ADHD), schizophrenia, and Parkinson’s disease. The presynaptic dopamine transporter (DAT) is a major control point for DA signaling and a key target for psychostimulants, including cocaine and amphetamine. DAT function is believed to be partly regulated through mechanisms supporting active shuttling between endosomal and cell surface membranes, and an extensive regulatory network providing post-translational control of DAT is beginning to emerge, although to date mostly based on in vitro data. We have chosen to pursue the goal of elucidating DAT regulatory mechanisms in the powerful model system Caenorhabditis elegans. The molecular machinery required for DA signaling is highly conserved in C. elegans and has been demonstrated to play an important role in egg-laying, locomotion, touch response, and defecation. The C. elegans DAT, DAT-1, modulates these behaviors by reuptake of DA from the synapse, limiting receptor availability and synaptic spillover of DA and enabling DA re-release following DA recycling to the presynaptic terminal. Our work has shown that DAT-1 activity is particularly important to ensure normal swimming behavior. Whereas wild-type worms thrash in water for up to 20 minutes at a relatively constant rate (~1 Hz), dat-1 mutants paralyze in a few minutes, a phenotype known as swimming-induced paralysis (Swip). In addition to forward genetic approaches, we are using quantitative methods to visualize the cellular localization DAT-1 by ratiometric comparison of DAT-1:GFP fluorescence in synapses, cell bodies, and dendrites using confocal microscopy. Using these methods, DAT-1 trafficking was found to depend on the DAT-1 C-terminus, as a Δ25 truncation resulted in somatic retention of the transporter and Swip. Mutagenesis efforts are underway to determine the minimal motif necessary for DAT-1 export. Recent data has shown that the ER export protein SEC24 participates in biogenic amine transporter folding and trafficking through a distal C-terminal motif so we also conducted mutagenesis studies to determine the role of this motif in proper DAT-1 trafficking. Mutation of the SEC-24 binding site in DAT-1 results in Swip and somatic retention of DAT-1:GFP. We are currently assessing which of the two SEC-24 orthologs present in C. elegans is responsible for ER export of DAT-1. Through these efforts, we hope to identify mechanisms required for proper DAT-1 export and synaptic localization and then translate our findings to mammalian DA neurons. Supported by NIH awards MH095044 to RDB, T32 MH065215 (S.B.), F31 MH093102 (A.H.), and MH095044 (R.D.B).
Identification of an Immunolocalization of Mblac1: Novel Glial Regulator of Extracellular Glutamate Homeostasis


Keywords: glutamate, dopamine, XC-, GLT1, MBLAC1

Glutamate plays a phylogenetically conserved role as a neurotransmitter from worms and flies to mice and humans. Synaptic glutamate levels are controlled by the activity of glutamate transporters expressed by astrocytes, including the Na+-dependent glutamate transporter GLT1 (EAAT2) and the glutamate/cystine exchanger XC-. Although of critical importance in buffering synaptic and extraneuronal glutamate for appropriate signaling as well as limiting the neurotransmitter's neurotoxic potential, the regulation of these transporters is poorly understood. In efforts to identify novel contributors to dopamine signaling via forward genetic methods in the nematode C. elegans, we discovered a gene, which we term swip-10. Genetic and imaging studies reveal that swip-10 functions in glia to regulate the expression of glutamate transporters that limit DA neuron excitation and DA release triggered by extracellular glutamate. Sequence analyses reveal that the mammalian ortholog of SWIP-10 protein is MBLAC1. Both genes contained a conserved metallo-beta-lactamase domain that, in the worm gene, contains the mutations recovered in our genetic screen. We have used PCR, in situ hybridization, western blots and immunocytochemical techniques to verify expression of Mblac1 mRNA and protein in the mouse brain. Our studies demonstrate a glial expression across the CNS, with enrichment evident in the prefrontal, cingulate, olfactory and pyriform cortex, as well as the striatum, nucleus accumbens, septum, amygdala and hippocampus. Immuno-electron microscopic analysis of MBLAC1 protein expression reveals enrichment in astrocytic leaflets that surround asymmetric synapses, consistent with regulation of glutamate transport. As prior studies have revealed that beta lactam antibiotics regulate expression of GLT1 and XC- in the rodent brain, we believe that MBLAC1 is the target for these effects. Ongoing genetic, imaging and biochemical studies seek to further explore how MBLAC1 coordinates glutamate transporter expression and extracellular glutamate homeostasis.

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Disruption of circadian behavior leads to insulin resistance and obesity

Shuqun Shi, Tasneem Ansari, Owen P McGuinness, David H Wasserman, Carl H Johnson

Keywords: circadian behavior, insulin resistance, obesity, 

Background: Disruption of circadian (daily) timekeeping enhances the risk of metabolic syndrome, obesity, and Type 2 diabetes. While clinical observations have suggested that insulin action is not constant throughout the 24 hour cycle, its magnitude and periodicity have not been assessed. Moreover, when circadian rhythmicity is absent or severely disrupted, it is not known whether insulin action will lock to the peak, nadir or mean of the normal periodicity of insulin action.

Results: We used hyperinsulinemic-euglycemic clamps to show a bona fide circadian rhythm of insulin action; mice are most resistant to insulin during their daily phase of relative inactivity. Moreover, clock-disrupted Bmal1-knockout mice are locked into the trough of insulin action and lack rhythmicity in insulin action and activity patterns. What’s more, disruption of circadian behavior by constant light exposure or lesion of suprachiasmatic nuclei (SCN) in brain also leads to decreased physical activity and increased weight gain.

Conclusions: This study provides rigorous documentation for a circadian rhythm of insulin action and demonstrates that disturbing the natural rhythmicity of insulin action will disrupt the rhythmic internal environment of insulin sensitive tissue. Meanwhile, this study also shows that animals with severely disrupted circadian behavior (feeding/fasting or wake/sleep) could be prone to obesity.
Galactose improves lipid metabolism in cultured SLOS fibroblasts and Dhcr7-deficient Neuro2a cells

Thiago C Genaro-Mattos, Sayuri Miyamoto, Karoly Mirnics, Ned A Porter, Zeljka Korade

Keywords: Cholesterol, Oxysterols, Gene expression

Culturing human dermal fibroblasts in reduced-lipid and galactose-containing media results in increased metabolic stress. In response to this stress, dermal fibroblast taken from healthy individuals change their mRNA and miRNA gene expression profile, and upregulate many transcripts critical for lipid metabolism. Interestingly, the same transcripts show a baseline expression difference in experimental models of Smith-Lemli-Opitz Syndrome (SLOS), a neurodevelopmental disorder caused by mutations in dehydrocholesterol reductase 7 (DHCR7) gene, an enzyme that converts 7-dehydrocholesterol (7-DHC) into cholesterol.

Based on these findings, we hypothesized that metabolizing galactose might improve the disrupted cholesterol metabolism seen in SLOS. We tested our hypothesis across two in vitro SLOS models: fibroblasts harvested from SLOS patients and Dhcr7-deficient Neuro2a cells. We found that replacement of glucose with galactose in the culturing media resulted in improved lipid profile in both SLOS fibroblast and Dhcr7-deficient Neuro2a cells. In addition to decreased 7-DHC levels, there was significant reduction in 7-DHC-derived toxic oxysterol production (DHCEO) in both SLOS models. Our results suggest that galactose consumption is preferentially changing cellular metabolism in cells with Dhcr7 mutations, and might normalize some of the critical molecular deficits related to SLOS pathophysiology.
TARGETED PROTEOMIC ANALYSIS OF SYNAPTIC AND EXTRASYNAPTIC GLUN2B-NMDA RECEPTORS FOLLOWING CHRONIC ETHANOL

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Keywords: Alcoholism, Hippocampus, Glutamate, NMDAR, Proteomics

One of the primary targets of ethanol is the NMDA receptor (NMDAR). Ethanol acutely inhibits NMDAR transmission, while chronic ethanol can increase NMDAR transmission. Our previous work demonstrated that in the bed nucleus of the stria terminalis (BNST) the acute inhibitory effects of ethanol and plasticity enhancing effects of chronic ethanol are specific to the GluN2B subunit. Our evidence suggests that chronic ethanol regulates extrasynaptic GluN2B-NMDARs. A GluN2B dependent localization shift has also been reported in hippocampal cultures, where chronic ethanol enhanced GluN2B-NMDARs synaptically then during early withdrawal these receptors moved to extrasynaptic localizations through lateral diffusion. To begin to investigate these regional- and ethanol-dependent changes, we have begun to employ a discovery-based proteomic approach to identify proteins that associate with GluN2B in synaptic and extrasynaptic locations in naive and chronic ethanol treated mice. We utilized samples from IPs for GluN2B, and all proteomic data were validated with samples from GluN2B knockout tissue to avoid non-specific interactions. We found a number of proteins involved in the homer signaling cascade that are modulated by chronic ethanol (homer 1, homer 2, GKAPs, Shank, and PSD proteins). Overall, ethanol produced pronounced apparent shifts in several proteins from the extrasynaptic fraction to the synaptic fraction. Further, several proteins found only in the extrasynaptic fraction of controls were present in the synaptic component following ethanol exposure. These data have begun to uncover the complex signaling mechanism involved in NMDAR dynamics following chronic ethanol.
Novel epilepsy-associated de novo mutations in GABAA receptor β3 subunit gene have different effects on GABAA receptor function.

Vaishali Satpute, Kelienne Verdier, Ningning Hu and Robert Macdonald

Keywords: Epilepsy, GABAA receptors, beta3 subunits, Epi4K

Epilepsy is the most common neurological disorder, characterized by unprovoked seizures. The prevalent form of epilepsy called Idiopathic generalized epilepsy, have been shown to have a genetic basis due to mutations in ion channel genes. Although, families with inherited epilepsies are invaluable for understanding the genetic basis of epilepsy, the majority of the patients do not have a clear pattern of inheritance in their families. However non-inheritable epilepsies are also thought to have a genetic component, which may occur due to spontaneous de novo mutations in the germline of the parents or somatic mutations in the embryo. Infantile spasms (IS) and Lennox-Gastaut syndrome (LGS)-two severe forms of childhood epilepsies with unaffected parents and unknown cause could represent noninheritable genetic epilepsies due to de novo mutations. The NIH funded Epi4K consortium recently identified four novel de novo mutations in the GABAA receptor β3 subunit gene, N110D from IS, and D120N, E180G and Y302C from LGS patients by whole exome sequencing, which could be epilepsy risk factors. GABAA receptors are the primary effectors mediating majority of inhibition in the brain, and β3 subunits are critical especially during neurodevelopment. Although the genetics of the patients is known, it is difficult to predict the effects of single nucleotide variations in the epilepsy genes. Thus in order to understand the molecular mechanisms by which these mutations might affect GABAA receptor function, we characterized the β3 subunit mutations in HEK293T cells. We found that the GABA evoked peak currents were significantly reduced for D120N, E180G and Y302C mutant β3 subunit containing GABAA receptors, but not for those with the N110D β3 subunits. Flow cytometry revealed that N110D and E180G β3 subunits have significantly increased surface levels as compared to the wild type β3 subunits, while D120N and Y302C surface levels are unaltered. Also, the total D120N and E180G β3 subunit levels are similar to the wild type, whereas N110D and Y302C β3 subunit levels are significantly higher. In conclusion the β3 mutations have different effects on function and expression of GABAA receptors. It is interesting to note that the N110D mutation found in patient with IS, a less form of epilepsy compared to LGS, does not affect GABA evoked peak currents in HEK293T cells. On the other hand the D120N, E180G and Y302C mutations found in LGS patients have a sever reduction of the peak GABA evoked currents. Further investigation is needed to understand the mechanisms by which the β3 mutations might contribute to epileptogenesis.
Poster: 35 Session: 1

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Overexpression of wildtype g2 subunits in mouse brain can reverse the impaired GABAergic neurotransmission in g2(Q390X+)/+ knock-in mice

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Keywords: GABRG2, epilepsy, mutation, GABAergic, rescue

Type A gamma-aminobutyric acid (GABA) receptor mutation, GABRG2(Q390X), is an epilepsy-associated mutation identified in a GEFS+ family. It generates a premature stop codon that disrupts assembly of gamma2 (g2) subunits into GABA receptors and affects trafficking of partnering alpha and beta subunits. Heterozygous g2(Q390X+)/+ knock-in mice showed reduced cortical inhibition, exhibited a lower seizure threshold and developed abnormal EEGs. In this study, we tried to rescue these defects of knock-in mice. We introduced an extra allele of GABRG2 by crossing g2(Q390X+)/+ knock-in mice with BAC transgenic mice overexpressing human g2 subunits in the mouse brain. Compared to the knock-in mice, mice carrying both the mutant allele and extra wildtype allele showed increased wildtype g2 subunit expression in the brain and increased mIPSC amplitude in cortical neurons. At the age of 4 months, the mutation-induced reduction of mIPSC amplitude and frequency recorded from cortical neurons were both reversed, comparable to those recorded from wildtype mice. We also measured the seizure threshold by injecting mice with pentylenetetrazol and found that at the age of 4 months, mice carrying both the mutant allele and extra wildtype allele exhibited a higher induced-seizure threshold compared to the knock-in mice. Our results suggested that the epilepsy phenotype caused by a GABRG2 mutation with dominant negative effects could be potentially rescued by increasing the expression of wildtype g2 subunits.
Role of inverse effectiveness in multisensory evidence accumulation

Aaron R. Nidiffer, Qing Qing Fheng, Mark T. Wallace

Keywords: Multisensory, decision making, evidence, inverse effectiveness,

In order to form a decision, sensory information is believed to accumulate over time until information reaches a decisional threshold. In a multisensory paradigm, the accumulation process includes information from each of the contributing sensory modalities. Although emerging work is beginning to outline the manner in which multisensory stimulus information is accumulated in order to reach a behavioral decision, significant gaps still exist in our knowledge of this process. One open question in this regard is how the well-established principle of inverse effectiveness, in which the pairing of weakly effective stimuli typically results in the largest proportional benefits, factors into multisensory decision making. To examine this question, subjects were asked to detect the presence of auditory white noise bursts, visual flashes from an LED, and combined audiovisual stimuli presented at five different intensity levels and four stimulus durations (200, 150, 100, and 50 ms). All stimuli were presented in the left peripheral field (-45°) while subjects fixated a central fixation cross, and all audiovisual combinations were spatially coincident and had a stimulus onset asynchrony (SOA) of 50 ms, auditory lagging. Subjects reported the presence of stimuli with a lever release in a yes-no paradigm and were instructed to release as quickly as possible while minimizing errors. Accuracy and reaction time data were collected and analyzed using signal detection theory and race model methods. In general, mean reaction times increased as stimulus level decreased, in agreement with standard evidence accumulation models. Reaction times and accuracy data revealed evidence for inverse effectiveness across stimulus durations: as duration decreased, subjects became faster and more accurate in detection. Similarly, race-model violations increased as stimulus level and duration decreased, and revealed similar multisensory benefits of combining very short duration and very low level stimuli. Behavioral benefits were greatest when stimuli were shortest and at the lowest intensity. These data provide support that evidence accumulation of multisensory information follows the principle of inverse effectiveness and serves to underline the ubiquity of this construct for multisensory processing.
How cortical responses to vowel categories reorganize across the early reading years: a longitudinal auditory ERP investigation of Mandarin lexical tone

Chang Gu, Micheal Sandbank, Han Wu, Hua Shu, Bruce McCandliss

Keywords: Categorical Perception, Mandarin Lexical Tones, Mismatch Negativity, longitudinal auditory ERP study

Categorical perception (CP) effects for speech contrasts that only occur in one particular language suggest learning experiences 'tune' the response properties of the auditory system. This two-year longitudinal ERP study investigates changes in pre-attentive auditory processing that underlies CP of Mandarin lexical tones during the years children learn to read fluently. Using a stimulus continuum spanning from one lexical tone category exemplar to another, we identified a 'between-' and a 'within category' tone deviant that were both were acoustically equidistant from a standard stimulus. 8-year-old Mandarin speakers participated in both an initial ERP oddball paradigm and returned for a two-year follow up. Mismatch negativity (MMN) responses demonstrated CP effects for both conditions at age 8. At age 10, however, between-category MMN responses showed reduced latencies and durations, and a shift toward a more adult-like topography. In contrast, the P3a component showed no evidence of CP in 8-year-olds. By age 10, these same participants demonstrated robust CP effects in their P3a responses. Clearly, the pre-attentive auditory processes underlying CP of Mandarin lexical tones have only partially developed by age 8. The ensuing two years, coincidental with the rise of fluent reading, provides a window into profound reorganization of the neural correlates of vowel category perception that include changes to both preconscious responses as well as P3a responses related to orienting to sound change. Finally, the degree of MMN topography shift toward adult-like predicts the amplitude of the P3a CP response of a child, providing a potential functional link between these components.
Involvement of the Serotonin Transporter in the Prenatal Actions of Cocaine?

Emily J. Ross, Randy D. Blakely, Gregg D. Stanwood

Keywords: Serotonin Transporter, Prenatal Cocaine, Neurodevelopment

Every year, thousands of pregnant women use cocaine. The effects of fetal cocaine exposure are not fully understood, but consequences include increased risks of preterm delivery, emotional dysregulation, and cognitive and behavioral deficits. While the brain dopamine transporter is often viewed as the most significant molecular target of cocaine, this "dirty" drug has high affinity for multiple proteins, including the serotonin and norepinephrine transporters. Because cocaine influences multiple neurotransmitters, it is difficult fully understand and study the developmental mechanisms impacted by fetal cocaine exposure.

Studies of structure-function relationships in the serotonin transporter (SERT) serendipitously led to the discovery of a single amino acid substitution that dramatically decreases the affinity of certain ligands for SERT (I172M). Knockin mice, expressing the I172M mutation have been generated that retain normal serotonin affinity and functional activity, but are ~50 fold less sensitive to cocaine. We are using this line to elucidate the role of serotonin in the effects of fetal cocaine exposure, through behavioral and neuroanatomical studies. We hypothesize that SERT I172M mice will exhibit milder deficits than wild types when exposed to fetal cocaine, with increased wild type impairments attributable to cocaine’s actions on serotonin levels. Understanding how SERTs are involved in the effects of fetal cocaine exposure may illuminate new mechanisms by which prenatal psychostimulants permanently alter brain structure and function, and lead to novel therapeutic approaches to restore normal neurodevelopmental trajectories.
Children with an inhibited temperament show altered amygdala-prefrontal cortex neurocircuitry prior to developing social anxiety disorder

Jacqueline A. Clauss, Suzanne N. Avery, Jennifer U. Blackford

Keywords: fMRI, inhibited temperament, anxiety, amygdala

Children with an inhibited temperament are quiet and cautious, and have a seven-fold increase in odds for in developing social anxiety disorder. Adults who were inhibited as children and adults with social anxiety disorder both have heightened amygdala and prefrontal cortex responses to social stimuli. It remains unknown whether amygdala responses to social stimuli are altered in inhibited children prior to the onset of social anxiety disorder. Twenty-six children ages 8-10 years were recruited. Children were identified as being extremely inhibited (n=11) or uninhibited (n=15) based on parent report. Children were excluded for any current psychiatric disorders or past psychiatric disorders, other than past separation anxiety disorder and specific phobia. Functional MRI was collected using a task to examine differences during anticipation of viewing fear faces, neutral faces, and neutral non-social stimuli. Seven minutes of resting state fMRI was also collected. During anticipation of social stimuli, inhibited children had increased amygdala and prefrontal cortex activation when anticipating viewing faces (fear or neutral), whereas uninhibited children had increased amygdala and prefrontal cortex activation only when anticipating viewing fear faces, relative to anticipating viewing neutral objects. These findings suggest that inhibited children readily anticipate and prepare to view both negative and neutral social stimuli. Inhibited children also had altered patterns of resting state connectivity. Inhibited children had reduced connectivity between the amygdala and dorsolateral prefrontal cortex. Reduced amygdala-prefrontal cortex connectivity has also been identified in adult anxiety disorders. These findings demonstrate that children at high-risk for developing anxiety already show alterations in amygdala and prefrontal cortex neurocircuitry. Early interventions, which alter these neural circuits, may prevent the development of disorders in at-risk children.
Visuotactile Illusions in the Schizophrenia-spectrum; implication for anomalous multisensory processing and the temporoparietal junction

J Michael, T Benson, A Nilsen, J Sondhi, S Park

Keywords: Multi-Sensory Processing

The temporo-parietal junction (TPJ) has been implicated as a neural area responsible for integrating sensory information, including visuospatial, proprioceptive, and tactile information. Abnormal multisensory integration is thought to play an important role in self disorders including dissociative experiences such out of body experiences (OBEs). However, the TPJ's role in multisensory integration in the context of OBEs and hallucinatory experiences in psychotic populations has not been carefully examined. Aspects of OBEs including malleable self-boundaries and impaired judgments about selflocation overlap with the phenomenology of hallucinations. We aim to examine multisensory processing in schizophrenia and schizotypy with a battery of visuotactile tasks. This will allow us to better understand whether or not sensory integration deficits in TPJ are central to schizophrenia.

The current study compares the performance of healthy controls and patients with schizophrenia (SZ) on a battery of visuotactile tasks designed to tap the underlying multisensory processes that may be abnormal in SZ. (1) The Pinocchio Illusion gauges susceptibility to perceive loosened self-boundaries and ambiguous spatial location of the body. (2) The Shape After Effect Illusion measures the tendency to take on a distorted perception of touch. (3) The Two Point Discrimination Task measures how sensitive participants are to perceiving tactile information. (4) The Graphesthesia Task indicates participants' abilities to comprehend symbols when presented in a tactile modality. (5) The Hand Reversal Task measures participants' abilities to integrate new and conflicting visual and proprioceptive information. (6) The Mental Rotation Task measures participants' abilities to perform mental transformations and adopt third person perspectives. Clinical symptoms are assessed with SANS and SAPS. In addition, a new questionnaire designed to probe anomalous bodily experiences (BODI) and the Perceptual Aberration Scale are used to assess the subjective experience of dissociation.

We hypothesize that SZ patients and healthy individuals with elevated schizotypal traits will be more susceptible to illusions than controls and will have increased ability to take on the third person perspectives during the mental rotation task. The outcome of the tactile illusions battery will be discussed.
Characterizing Resting State Functional Connectivity in Individuals with Down Syndrome and Williams Syndrome Compared to Healthy Controls.

Keywords: Down Syndrome, Williams Syndrome, Functional Connectivity

Background: The emergence of resting-state functional connectivity (rsFC), which examines temporal correlations of low-frequency (< 0.1Hz) BOLD signal fluctuations between brain regions, has dramatically improved our understanding of the functional architecture of the typically developing (TD) human brain. However, no published study has characterized rsFC in Down syndrome (DS) compared to Williams syndrome (WS).

Methods: The current study included 10 DS subjects without dementia (6 females, 4 males; mean age 38.9), 18 WS subjects (5 females, 13 males; mean age 25.8), 40 TD subjects (16 females, 24 males; mean age 46.9). Each subject participated in a 55-minute MRI scan in a Philips Achieva 3T scanner with an 8 channel head coil. A gradient echo echoplanar pulse was used to collect the resting state T2* weighted images in the absence of external stimuli while the subject was awake with eyes closed. High-resolution 3D anatomical T1W images were acquired using a turbo field echo pulse sequence with full brain coverage for co-registration with fMRI. We compared between and within network rsFC connectivity using a published parcellation of the brain into 7 functional networks by Yeo et al. (2011). Independent samples t-tests were used to examine group differences in within and between network connectivity (DS vs TDs and DS vs WS).

Results: We detected statistically significant (corrected p< 0.05) differences in within network connectivity in DS compared to WS. In particular, DS showed significantly greater within network connectivity compared to WS in (a) default mode network (DMN; t(26)=3.38, p< 0.05) and (b) visual network (t(26)=3.39, p< 0.05). There were no significant differences (once corrected for multiple testing) in within network connectivity when comparing the DS and TD groups. We also detected statistically significant (corrected p< 0.05) differences in between network connectivity in DS compared to TD controls in 6/21 network pairs. In particular, DS showed significantly greater between network connectivity compared to TD controls in the following network pairs: (a) Visual-Executive (t(48)=4.83, p< 0.05), (b) Somatomotor-Executive (t(48)=3.45, p< 0.05), (c) Somatomotor-DMN (t(48)=3.68, p<0.05), (d) Dorsal Attention Network (DAN)-Executive (t(48)=4.95, p< 0.05), (e) DAN-DMN (t(48)=4.30, p< 0.05), and (f)Limbic-DMN (t(48)=3.18, p< 0.05). There were no significant differences (once corrected for multiple testing) in between network connectivity when comparing the DS and WS groups.

Conclusions: We present evidence of increased within network connectivity in DS compared to WS and increased between network connectivity in individuals with DS compared to TD controls. Recruitment is ongoing, and analyses incorporating cognitive data and APOE status are forthcoming.
The koniocellular pathway exhibits a unique distribution of glutamate related proteins

Roan T. Marion, Moses Koo, Jay P. Patel, Ashley E. Wenger, Eesha Singh, Julia A. Mavity-Hudson, Vivien A. Casagrande,

Keywords: Koniocellular, Modulatory, mGluR2

The pulvinar has reciprocal connections with early visual cortices, including the primary (V1) & secondary visual cortex as well as MT, in all studied primates. MT receives its main input from the superficial layers of V1, while also receiving from V2, the inferior pulvinar, and interlaminar lateral geniculate nucleus (LGN). In both bush baby and macaque, neighboring subnuclei of pulvinar project to MT and receive input from the superior colliculus (SC). Some pulvinar neurons also have been shown to directly connect SC with MT. It has been speculated that this SC-pulvinar-MT pathway underlies the residual unconscious vision in patients that lack V1. We recorded extracellularly from layer II/III cells in the central representation of MT with a Utah array (Blackrock) in 7 anesthetized, paralyzed bush babies (Otolemur garnettii) while manipulating the activity in ipsilateral pulvinar with large injections of glutamate (500 - 1000nl, 1M) or muscimol (500nl, 66.7mM) mixed with biotinylated dextran (10k WM, 2%). These pressure injections were placed in pulvinar with visual field representations overlapping those of the recorded MT cells, without spreading into the lateral geniculate nucleus or SC. The dextrean label was used to confirm the injections. 100% coherent random dot kinetograms were used as visual stimuli. In 2 of the cases, central V1/V2 was block with muscimol (100 μl, 100mM) before glutamate injection in the pulvinar. An increase was observed in both spontaneous and visually driven activity after glutamate injection in the pulvinar, suggesting that pulvinar can impact activity in the intact visual system. The increase appeared immediately after injection and lasted 3-5 minutes. Additionally, a decrease in visually evoked activity was observed in MT 15 minutes after muscimol injection in the pulvinar indicating that pulvinar input may be important to achieving normal levels of visually driven activation in MT. However, these effects appear to rely on a V1 relay. After muscimol blocking of V1, MT neurons retained around 50% of their normal activity, and showed a further drop in activity following glutamate injection in the either dorsal map of lateral pulvinar or the medial inferior pulvinar. Although previous studies have shown anatomically and electrophysiologically that connections exist between the pulvinar and MT, this is the first study to demonstrate that the level of activity in the pulvinar has a direct effect on the visually driven activity in MT.
Causal Control of Medial-Frontal Cortex Improves Performance Monitoring and Learning in Schizophrenia

Julia Q. Zhu, Robert Reinhart

Keywords: medial-frontal cortex, executive control, learning, transcranial direct current stimulation

The medial-frontal cortex has an important role in adaptive human behavior and the pathophysiology of various neuropsychiatric disorders like schizophrenia. To date, the primary means of influencing this brain region has been with pharmacological interventions or implanted electrodes. Here we introduce a novel noninvasive brain stimulation protocol to remediate dysfunctional neural circuitry underlying the executive control deficits in schizophrenia. Using transcranial direct-current stimulation (tDCS) of the medial-frontal cortex, we were able to selectively increase patients' performance-monitoring activity and cause improvements in behavioral accuracy, the compensatory behavior following an error, and learning rates. Patients with the greatest gains in performance-monitoring activity after stimulation showed the greatest improvements in behavior and executive control. These results suggest that medial-frontal brain stimulation can provide immediate treatment of neuropsychiatric illnesses for which disrupted executive functioning is a major source of widespread cognitive impairment.
Local field potentials reveal novel multisensory interactions in cat insular cortex

Juliane Krueger Fister, LeAnne R. Kurela, Aaron R. Nidiffer, Walter H. Lee, Troy A. Hackett, Mark T. Wallace

Keywords: multisensory, multielectrode, insula

Multisensory interactions have been well described at the spiking level in both cortical and subcortical structures, and generally entail changes in firing rate that differ significantly from those predicted by knowledge of unisensory firing patterns. Much less is known about the synaptic processes that likely give rise to these differences in spiking. In the current study, we focused on the insular cortex in the cat that is a watershed site for multisensory convergence, and employed local field potentials (LFPs) to begin to detail multisensory interactions beyond those that are visible in spiking patterns. A 16-channel multilaminar electrode was introduced into cortex and multiunit activity (MUA) and LFPs were recorded. The spatiotemporal structure of the receptive fields and response profiles were investigated by delivering unisensory (i.e., visual alone, auditory alone) and multisensory (i.e., visual-auditory) stimuli that varied in spatial location and in temporal relationship (stimulus onset asynchrony or SOA). Both MUA and LFP analyses revealed the presence of multisensory interactions throughout the insula. Often, these interactions were most visible in the LFP traces, in which the recorded LFP signals under multisensory conditions frequently exceeded the addition of the unisensory voltage signals (or the maximum unisensory voltage signals), suggesting the presence of substantial multisensory processing at the synaptic level. Furthermore, the nature of these interactions was strongly shaped by the spatial and temporal relationships of the paired stimuli, and showed a complex spatiotemporal architecture to cortical multisensory processing. In addition, the patterns of interaction varied greatly depending on presumed supra- versus infragranular recording location, and will be further explored in current source density (CSD) analyses. Collectively, these results demonstrate the presence of widespread multisensory interactions in the insula, and highlight the utility of the LFP in elucidating both the extent and spatiotemporal structure of cortical multisensory interactions.
Human psychophysical and animal behavioral studies have illustrated the benefits that can be conferred from having information available from multiple senses. Given the importance of multisensory integration for perceptual and cognitive abilities, it has become imperative to extend the design of behavioral paradigms used in animal models in order to provide important mechanistic insights into the neural bases of these multisensory processes. While prior behavioral studies of multisensory processing have focused on large mammalian models (e.g., cat, monkey), the mouse offers a host of advantages over these species, including cost, maturational timeline and the ability to perform genetic manipulations that have relevance for human disease processes. However, in order to begin to employ this model species for multisensory research, it is necessary to first establish a robust behavioral assay of multisensory processing in this species - the goal of the current study. Nine animals from two different commonly used mouse strains (C57BL/6J and 129S6/SvEv) were trained to respond to unisensory (visual and auditory) stimuli in order to receive a liquid reward using classic operant shaping methods. After training was completed for these conditions, the visual and auditory stimuli were then either presented individually or paired in a congruent fashion. The degree of multisensory interaction was then measured in terms of accuracy, reaction times, and percent gain on paired (audiovisual) trials. Both strains of animals were capable of performing this task for both the visual and auditory only training conditions. In addition, preliminary evidence shows that multisensory pairings result in performance gains of up to 19%. Experiments are currently in progress to decrease the intensity and duration of the unisensory stimuli, with the expectation that the pairing of these less effective stimuli will result in even larger multisensory gains. Collectively, these results are the first to validate the mouse as a species that shows demonstrable behavioral facilitations under multisensory conditions, and opens up enormous opportunity for future mechanistically directed studies of the neural bases of multisensory integration.
Executive Function (EF) is a critical component of successful reading comprehension, and yet the specific neurobiological relationship between these higher order cognitive skills and reading comprehension is poorly understood. Behavioral studies indicate that, compared to other text types, expository text comprehension specifically places greater demand on EF, particularly working memory, planning/organization, and inference processes (Eason, 2012). Expository text is consequently a unique environment in which to study the interaction between EF and reading comprehension, however no imaging studies to date have examined the neural correlates of expository text comprehension. In our study, we observed 41 adolescents (10-14 yrs) with normal word efficiency scores (TOWRE score between 85-115), while they comprehended single words and expository text in the fMRI. First, we sought to identify the neural underpinnings of expository text comprehension using a General Linear Model (GLM) analysis. These results suggest that, in addition to traditional left-lateralized language regions, adolescent readers rely on bilateral angular gyrus, posterior cingulate cortex, and temporal poles, as well as left-lateralized medial prefrontal cortex-- all higher order processing regions previously implicated in both narrative comprehension and EF studies-- when reading expository texts. Additionally, by running a covariate analysis on two non-linguistic measures of general EF ability, we found that higher working memory scores result in less activity in medial prefrontal cortex, while higher planning/organizational scores correlate with less activity in the left dorsolateral prefrontal cortex. This suggests that higher EF scores may result in greater efficiency (less activation) in frontal lobe EF regions during adolescent reading comprehension.
Pulvinar affects the middle temporal area (MT) activity in primate

Keji Li, Gopathy Purushothaman, Roan T Marion, Yaoguang Jiang, Dmitry Yampolsky, Julia M Mavity-Hudson, Vivien A Casagrande

Keywords: PRIMATE, PULVINAR, MIDDLE TEMPORAL CORTEX

The pulvinar has reciprocal connections with early visual cortices, including the primary (V1) & secondary visual cortex as well as MT, in all studied primates. MT receives its main input from the superficial layers of V1, while also receiving from V2, the inferior pulvinar, and interlaminar lateral geniculate nucleus (LGN). In both bush baby and macaque, neighboring subnuclei of pulvinar project to MT and receive input from the superior colliculus (SC). Some pulvinar neurons also have been shown to directly connect SC with MT. It has been speculated that this SC-pulvinar-MT pathway underlies the residual unconscious vision in patients that lack V1.

We recorded extracellularly from layer II/III cells in the central representation of MT with a Utah array (Blackrock) in 7 anesthetized, paralyzed bush babies (Otolemur garnettii) while manipulating the activity in ipsilateral pulvinar with large injections of glutamate (500 - 1000nl, 1M) or muscimol (500nl, 66.7mM) mixed with biotinylated dextran (10k WM, 2%). These pressure injections were placed in pulvinar with visual field representations overlapping those of the recorded MT cells, without spreading into the lateral geniculate nucleus or SC. The dextrean label was used to confirm the injections. 100% coherent random dot kinetograms were used as visual stimuli. In 2 of the cases, central V1/V2 was block with muscimol (100μl, 100mM) before glutamate injection in the pulvinar.

An increase was observed in both spontaneous and visually driven activity after glutamate injection in the pulvinar, suggesting that pulvinar can impact activity in the intact visual system. The increase appeared immediately after injection and lasted 3-5 minutes. Additionally, a decrease in visually evoked activity was observed in MT 15 minutes after muscimol injection in the pulvinar indicating that pulvinar input may be important to achieving normal levels of visually driven activation in MT. However, these effects appear to rely on a V1 relay. After muscimol blocking of V1, MT neurons retained around 50% of their normal activity, and showed a further drop in activity following glutamate injection in the either dorsal map of lateral pulvinar or the medial inferior pulvinar. Although previous studies have shown anatomically and electrophysiologically that connections exist between the pulvinar and MT, this is the first study to demonstrate that the level of activity in the pulvinar has a direct effect on the visually driven activity in MT.
Menstrual Phase is Associated with Difference in Brain Activity during Psychosocial Stress

Kimberly M. Albert

Keywords: Menstrual Cycle, Ovarian Hormones, Estrogen, Stress, fMRI

Compared to men, there is a higher incidence of depression in women, beginning in puberty and continuing to menopause. Gender differences in reactivity to stressful events, specifically vulnerability to social stress in women, may underlie the gender difference in depression risk. Because this increased risk for mood disorders in women occurs during the reproductive phase of life, gonadal hormones are presumed to be involved, and differences in stress reactivity may be associated with menstrual phase in normally cycling women. The primary aim of this study was to examine the brain activation and deactivation patterns, using fMRI, associated with the response to psychosocial stress in women during menstrual phases with differing levels of estradiol (E2).

Twenty two women (average age 31.7 years) with regular menstrual cycles and no form of contraceptive medication, completed the Montreal Imaging Stress Test (MIST). This is an fMRI paradigm designed to induce psychosocial stress via difficult mental arithmetic and negative social evaluation. The women were randomized to two groups, with ten women completing the task during a high E2 phase (late follicular) of the menstrual cycle and twelve women completing the task during a low E2 phase (late luteal) of the menstrual cycle. Previously, the MIST has been shown to induce consistent patterns of activation in dorsal prefrontal cortex (PFC) regions, and deactivations in ventral PFC, and medial temporal lobe regions, linked with an increase in cortisol levels.

fMRI results for all subjects showed limbic deactivation during the stress condition of the task, consistent with findings from previous studies using the MIST. Between group contrasts for estradiol level revealed a difference in left hippocampus activation, with the high E2 group showing greater activity compared to the low E2 group. Additionally, the low E2 group showed greater distress following the MIST than the high E2 group. Between group contrasts for subjective distress revealed less bilateral hippocampus activity and greater subgenual cingulate activity for the high distress group compared to the low distress group. Additionally, greater distress was associated with greater negative mood and lower estradiol levels. The hippocampus has been associated with regulation of the autonomic stress response and modulation of emotional states. Greater activity in the hippocampus, in the high E2 compared to low E2 group, during an acute psychosocial stressor, suggests that estradiol may modulate activity in brain systems related to autonomic and emotional control. These results provide support for a role for estradiol in modulating the stress response.
The effect of visual deprivation on multisensory integration in the cat superior colliculus

LeAnne R Kurela, Juliane K Fister, Aaron R Nidiffer, Mark T Wallace

Keywords: multisensory, superior colliculus, cat, sensory deprivation,

Combining information from different sensory modalities is a prerequisite to navigate the world around us. The superior colliculus (SC) is a critical hub for multisensory processing, and has been shown to play an integral role in orientation behaviors. Previous research has revealed that over half of the neurons in the intermediate and deep layers of the cat SC receive convergent information from two or more sensory modalities, and that many of these transform these different inputs. Developmental studies have shown that multisensory SC neurons mature gradually during early postnatal life, and that this maturation is critically dependent upon sensory experience. For example, complete elimination of visual experience via dark-rearing results in the inability of SC cells to integrate their multisensory input. Restoration of visual experience in adulthood had relatively minimal effects on multisensory processing, with most neurons still lacking integrative capacity and suggesting the presence of a critical or sensitive period for multisensory experience. If such is the case, then changes in sensory experience in adulthood should have little effect on multisensory processing. To examine this question, cats were reared under normal lighted conditions until adulthood. At 6 months of age they were transferred to a visually deprived environment and remained there for an additional 6 months. Extracellular recordings of local field potentials (LFP) and multi-unit activity (MUA) recorded from the intermediate and deep layers of SC were then performed. These experiments revealed that although multisensory integration remains in many neurons following adult visual deprivation, the response characteristics of these neurons were altered from normally-reared animals. Most apparent in this regard were changes in the temporal dynamics of the unisensory (visual, auditory) and multisensory responses. Collectively, these findings not only provide support for the concept of a critical period for multisensory development, but also show that adult experience is important for the preservation of normal response properties in these neurons.
Differences in age-related effects on brain volume in Down syndrome as compared to Williams syndrome and typical development

Mary Ellen I. Koran, Timothy J. Hohman, Jennifer N. Vega, Jennifer R. Pryweller, Laura E. Slosky, Genea Crockett, Lynette Villa de Rey, Courtney M. Edwards, Shashwath A. Meda, Suzanne N. Avery, Jennifer U. Blackford, Elisabeth M. Dykens, Tricia A. Thornton-Wells

Keywords: Down syndrome, Williams syndrome, brain volume, accelerated aging, APOE

Background: Individuals with Down Syndrome (DS) are reported to experience accelerated brain aging. However, it is not well understood how pre-existing neurodevelopmental effects versus neurodegenerative processes might be contributing to the observed pattern of brain atrophy in younger adults with DS. The aims of the current study were to: (1) to confirm previous findings of accelerated aging in DS compared to adults with typical development (TD), (2) to test for an effect of accelerated aging in a second neurodevelopmental disorder, Williams syndrome (WS), and (3) to identify a pattern of regional age-related effects that are unique to DS.

Methods: High-resolution T1-weighted MRI brain images of subjects with DS, WS, and TD controls were segmented, and estimates of regional brain volume were derived using Freesurfer. A general linear model was employed to test for age-related effects on volume between groups. Secondary analyses in the DS group explored the relationship between brain volume and neuropsychological tests.

Results: Consistent with previous findings, the DS group showed significantly greater age-related effects relative to TD controls in total grey matter and in regions of the orbitofrontal cortex and the parietal cortex. Individuals with DS also showed significantly greater age-related effects on volume of the left and right inferior lateral ventricles (LILV and RILV, respectively). There were no significant differences in age-related effects on volume when comparing the WS and TD groups. In the DS group, cognitive tests scores measuring signs of dementia were significantly associated with LILV and RILV volume.

Conclusions: Individuals with DS demonstrated a unique pattern of age-related effects on grey matter and ventricular volume, the latter of which was strongly associated with dementia rating scores in the DS group. Results support the hypothesis that accelerated brain aging in DS is primarily due to neurodegenerative processes, as opposed to pre-existing neurodevelopmental differences.
Bidirectional causal control of human performance monitoring and learning

Robert MG Reinhart, Geoffrey F Woodman

Keywords: executive control, performance monitoring, learning, transcranial direct-current stimulation,

Adaptive human behavior depends on the capacity to adjust cognitive processing after an error. Here we show that transcranial direct-current stimulation of medial-frontal cortex provides causal control over the electrophysiological responses of the human brain to errors and feedback. Using one direction of current flow, we eliminated performance-monitoring activity, reduced behavioral adjustments following an error, and slowed learning. By reversing the current flow in the same subjects, we enhanced performance-monitoring activity, increased behavioral adjustments following an error, and sped learning. These beneficial effects fundamentally improved cognition for nearly 5 hours following 20 minutes of noninvasive stimulation. The stimulation selectively influenced the potentials indexing error and feedback processing without changing potentials indexing mechanisms of perceptual or response processing. Our findings demonstrate that the functioning of mechanisms of cognitive control and learning can be up or down regulated using noninvasive stimulation of medial-frontal cortex in the human brain.
Classroom Noise and Fatigue in Children with Normal Hearing and Children with Hearing Loss

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Keywords: Hearing loss, children, cortisol, noise,

Children with hearing loss experience greater difficulty understanding speech in noise and in reverberant conditions. The effortful hypothesis posits that individuals with hearing loss are required to invest greater processing resources when identifying speech when compared to listeners with normal hearing. This reduction in available processing resources is thought to cause increased listening effort, stress and fatigue. The purpose of this study was to determine if school-aged children with hearing loss show different patterns of stress and fatigue when compared to children with normal hearing. A secondary purpose was to examine if classroom noise level has an effect on stress and fatigue in children with hearing loss and children with normal hearing. Children with hearing loss showed elevated cortisol awakening responses, suggesting the possibility of chronic stress and subsequent fatigue. Classroom noise levels did not appear to affect changes in cortisol levels from morning to afternoon. Although cortisol levels are expected to fall through the day, preliminary data suggest this pattern may be reversed for some children with hearing loss.
Executive Function (EF) is a critical component of successful reading comprehension, and yet the specific neurobiological relationship between these higher order cognitive skills and reading comprehension is poorly understood. Behavioral studies indicate that, compared to other text types, expository text comprehension specifically places greater demand on EF, particularly working memory, planning/organization, and inference processes (Eason, 2012). Expository text is consequently a unique environment in which to study the interaction between EF and reading comprehension, however no imaging studies to date have examined the neural correlates of expository text comprehension. In our study, we observed 41 adolescents (10-14 yrs) with normal word efficiency scores (TOWRE score between 85-115), while they comprehended single words and expository text in the fMRI. First, we sought to identify the neural underpinnings of expository text comprehension using a General Linear Model (GLM) analysis. These results suggest that, in addition to traditional left-lateralized language regions, adolescent readers rely on bilateral angular gyrus, posterior cingulate cortex, and temporal poles, as well as left-lateralized medial prefrontal cortex-- all higher order processing regions previously implicated in both narrative comprehension and EF studies-- when reading expository texts. Additionally, by running a covariate analysis on two non-linguistic measures of general EF ability, we found that higher working memory scores result in less activity in medial prefrontal cortex, while higher planning/organizational scores correlate with less activity in the left dorsolateral prefrontal cortex. This suggests that higher EF scores may result in greater efficiency (less activation) in frontal lobe EF regions during adolescent reading comprehension.
Semantic verbal fluency predicts mathematical learning

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Keywords: mathematics learning, individual differences, cognitive processes, ,

Differences in young children's cognitive abilities predict later academic achievement (Welsh et al., 2010). For instance, working memory has been shown to be important for performance on various mathematical tasks (see Raghubar et al., 2010). Another key cognitive process for learning may be semantic verbal fluency (i.e., fluency), or the controlled search and retrieval of words from long-term memory (Baddeley, 1996). Fluency has been shown to predict both concurrent and future mathematics performance (Andersson, 2008; Swanson, 2011). The ability to strategically search and retrieve information from memory may help students better attend to, process, and apply instructional guidance. However, to our knowledge, no previous research has investigated the combined influence of working memory and fluency in math learning.

We examined the contributions of fluency and working memory to elementary school children's understanding of math equivalence (i.e., quantities on both sides of the equal sign have the same value), a critical concept for learning algebra (Carpenter et al, 2003). We used a pretest-intervention-posttest design, including a 2-week retention test. During the intervention, 122 second and third grade students solved math equivalence problems (e.g., \(4 + 5 + 8 = ? + 8\)) and received conceptual instruction on the meaning of the equal sign.

Math equivalence knowledge was measured using an 18-item assessment (Rittle-Johnson et al., 2011). In addition, working memory was assessed with the backward digit and backward letter span tasks (Davis & Pratt, 1995), and fluency was measured with a task adapted from the NEPSY II (2007), in which children were given 1 minute each to name as many items as possible from two semantic categories (i.e., animals and food). Controlling for grade and prior math equivalence knowledge, hierarchical regression models indicated that students' mathematical equivalence knowledge was significantly predicted by both working memory (\(\beta = .20, p < .05\)) and fluency (\(\beta = .21, p < .01\)) at posttest. However, at the retention test, students' working memory was no longer significant (\(\beta = .08, p > .05\)), whereas fluency (\(\beta = .22, p < .01\)) still predicted math equivalence.

Findings indicate that while both working memory and fluency seem to impact immediate learning of math equivalence, only fluency remains important for knowledge retention. Supplemental analyses will explore the aspects of learning that fluency appears to influence the most. For example, does fluency influence children's ability to encode important features of problems? Future mathematics studies with young children should account for the dynamic relations between different aspects of cognitive ability to better understand the role of individual differences in children's math learning.
Poster: 55 Session: 1

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Parent Training for Young Children: A Systematic Review of the Literature

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Keywords: Parent training, Social emotional competence, Problem Behavior

Experts estimate the prevalence of challenging behavior among young children is 10-25% and the rate is even higher in children whose families have a low-income (Kaiser, Cai, Hancock, & Foster, 2002; Webster-Stratton & Hammond, 1998). There are a number of ecological risk factors in the home and community that are predictive of children engaging in challenging behavior. Familial risk factors include: low maternal education (Halle et al., 2009), maternal depression (Civic & Holt, 2000), maternal stress (Fossum, Morch, Handegaard, & Drugli, 2009), low socioeconomic status (Qi & Kaiser, 2003), parental anxiety and depression (Hastings, 2002; Seltzer et al., 2010), and a parental negative view of children (Durand, Hieneman, Clarke, Wang, & Rinaldi, 2013). Having a child with challenging behavior can be stressful to parents, which can lead to increased negative interactions with their children (Durand et al., 2013). Parenting interventions are a low-cost way to improve the quality of parent-child interactions and promote children's social-emotional skills, while also reducing challenging behavior (Kazdin, 1997). Parent trainings are thus, a widely used intervention to decrease problem behaviors in young children. In the present study a systematic review of the literature on the use of the group parent trainings to decrease problem behavior and increase social-emotional competence of young children (ages 3-8) was conducted. Studies were then coded to assess the quality of study, participant and study characteristics, and findings. Meta-analytic procedures were then used to calculate the standardized mean difference for each study and the overall sample. Moderator analysis to assess the effects of length of treatment, maternal education, and other risk factors and the effects on young children's challenging behavior were conducted. Publication bias and sensitively analysis were conducted and resulted in no likely publication bias present or adjustments needed. Recommendations for research and practice are discussed. Additional research using more rigorous methodology from more research groups for each training curriculum is needed.
A Meta-Analysis of Student Response Accuracy on Comprehension Measures

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Keywords: reading, comprehension, learning disabilities, meta-analysis,

In recent years, researchers have dedicated increased attention to the task sensitivity of reading comprehension measures and how different groups of students perform on various types of measures (Cain & Oakhill, 2006; Griffo, 2012). The purpose of the current study was to answer two research questions: (a) When compared to typically developing (TD) students, do students with learning disabilities (LD) or reading difficulties (RD) vary in response accuracy across different measures of reading comprehension (e.g., multiple choice, cloze)? (b) Do different study variables moderate students' performance on specific types of reading comprehension tasks? A systematic review of the existing literature identified eligible studies for inclusion in this meta-analysis. Eligible studies included participants in kindergarten through twelfth grade with one group of students identified as LD and a comparison group of TD peers. The Hedge's g standardized mean difference effect sizes were calculated for all studies, and a random effects model was applied to aggregate the effect sizes for specific comprehension tasks (Borenstein, Hedges, Higgins, & Rothstein, 2009). Random effects meta-regression analyses were also used to investigate the secondary research question and explore potential moderators of the study effect sizes. Preliminary results indicated the achievement gap between students with LD and TD peers was larger for some comprehension measures (e.g., multiple choice comprehension tasks ESg = -2.36) than others (e.g., cloze procedures ESg = -1.14). However, the analyses also revealed a large amount of heterogeneity in the effect sizes. Surprisingly, the random effects metaregression models including the classification of LD (e.g., poor decoders, poor comprehenders) and specific reading measures as moderators failed to explain the variability in the effect sizes. Therefore, other study factors may contribute to the heterogeneity observed in the effect sizes. Overall, the metaanalysis results suggest students with LD may perform poorer on comprehension tasks that require multiple cognitive processes than measures that place less cognitive demands on the reader. Consequently, in an era with high-stakes testing, the variations in the performance of students with LD on different reading comprehension tasks should be considered when making important policy decisions and evaluating the effectiveness of reading interventions.
Comparing the Performance Characteristics of ASD Screening Measures in Toddlers

Amanda L Palmer, Alison C Vehorn, Zachary E Warren

Keywords: Autism, Screening, Early detection,

Background: In an effort to lower the age of diagnosis and take advantage of early intervention services, the American Academy of Pediatrics recommends universal screening for ASD beginning at 18 months. The most widely used screening measure, the Modified Checklist for Autism in Toddlers (M-CHAT), has been shown to identify many children with ASD at young ages, but often results in substantial overidentification of children with other developmental concerns, particularly when clinicians do not utilize the embedded follow-up interview (Chlebowski et al., 2013; Miller et al., 2011). This over-identification is particularly problematic given that most tertiary assessment centers struggle to provide diagnostic assessment without substantial waits.

Objective: To determine if a new screening instrument, the Vanderbilt Scales for ASD, utilizing graded parental ratings, would possess improved performance characteristics over the M-CHAT in accurately identifying children with and without ASD. The Vanderbilt Scales for ASD consists of 23 items, from developmental checklists and interviews commonly used at Vanderbilt clinics, which were determined to have the highest weights in the ASD population. We also investigated the incremental clinical value of use of a structured observation of behavior in conjunction with the parent report screening measures.

Methods: Participants included 161 children, 18-36 months, participating in autism research protocols at a university based autism clinic. Examined measures included the M-CHAT, Vanderbilt Scales for ASD, and Autism Diagnostic Observation Schedule (ADOS). Three items from the ADOS that could potentially be easily administered by community clinicians were chosen as a structured observation of behavior. Sensitivity, specificity, and positive predictive value (ppv) were calculated for each screening measure as well as the simultaneous testing of each screening measure with the three ADOS items.

Results: Reliability analysis of the Vanderbilt Scales for ASD yielded a cronbach's alpha of .803. A cutoff score of 9 on the Vanderbilt Scales resulted in sensitivity= 80.65%, specificity= 66.18%, and ppv= 76.53%. M-CHAT: sensitivity= 87.10%, specificity=52.94%, and ppv= 71.68%. Screen positive on both the Vanderbilt Scales and ADOS items: sensitivity= 77.22%, specificity= 86.54%, and ppv= 89.71%. Screen positive on both the M-CHAT and ADOS items: sensitivity= 75.28%, specificity= 83.61%, and ppv= 87.01%.

Conclusions: The Vanderbilt Scales was slightly less sensitive than the M-CHAT, but resulted in a higher specificity and ppv. Simultaneous testing requiring positive screening on both the ADOS and screening measure resulted in a higher ppv than when either respective screening measure was used alone. These results suggest further investigation into the use of a parent report measure, clinician follow-up, and structured observation of behavior to identify children in need of an autism specific evaluation.
Early Predictors of Parental Linguistic Mapping in Preschoolers with Autism Spectrum Disorders

Bahar Kecili Kaysili, Amy Tostanoski, Paul Yoder

Keywords: autism spectrum disorders, early childhood, speech development

Background. Parents may interpret children's frequent use of triadic attention (i.e., coordinated attention to communicative partner and referent) as indicating readiness for linguistic responses, which may facilitate language development. Triadic attention includes attention following and intentional communication. Parental linguistic mapping (PLM) occurs when parents immediately say the presumed meaning of children's communication acts. PLM frequency predicts later language in several populations of children with disabilities, including ASD. Identifying predictors for PLM provides one piece of evidence for identifying pivotal skills for language development in children with ASD.

Objectives. Predictive relations were examined between (a) early frequency of intentional communication and attention following and (b) later frequency of PLM.

Methods. The study used a longitudinal correlational design, with 3 assessment periods over 12 months. Our project provided no treatment during the study, though participants could get treatment. Eighty-one minimally-verbal preschoolers (age M = 35.2 months, SD= 7; mental age M = 12.3 months, SD = 5) participated. All children received a clinical diagnosis of autism (95.1%) or PDD-NOS (4.9%) from a licensed psychologist who used gold standard instruments and clinical best judgment according to DSMIV-TR criteria. Attention following and intentional communication skills were measures at Time 1 and Time 2 (4 months after Time 1) using the Communication and Symbolic Behavior Scale, Early Social Communication Scales, and responsive examiner-child language samples. PLM frequency was measured at Time 2 and Time 3 (8 months after Time 2) using a semi-structured 10-minute parent-child snack session. Two multiple regression analyses were conducted using PLM frequency at Time 2 as a control variable, each triadic attention skill as the predictor variable, and PLM frequency at Time 3 as the criterion variable.

Results. Initial frequency of PLM (partial r = .44) and early attention following (partial r = .27) predicted later frequency of PLM, R2=0.29, p<0.01. Initial PLM frequency (partial r = .45) and early intentional communication (partial r = .25) predicted later PLM frequency, R2=0.28, p<0.01.

Conclusion. Results are consistent with the hypothesis that the two triadic skills may encourage PLM. Identifying predictors of PLM may sensitize parent trainers to reasons parents vary in their use of PLM. It is possible that teaching parents to use follow-in utterances (i.e., talking about children's attentional focus) may be a more adaptive parental skill during times when their children are not using triadic skills frequently. Past research on preschoolers with ASD found PLM predicted later vocabulary only if children had a threshold level of comprehension, a probable correlate of triadic attention. Meanwhile, follow-in utterances predicted language across comprehension levels (McDuffie & Yoder, 2010).
Depression and Autism

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Keywords: Autism, Depression

Research suggests that depression is among the most common psychiatric problems associated with autism spectrum disorder (ASD) across the lifespan. We sought to identify medical and behavioral problems associated with a history of depression in children and adolescents with ASD. A data set including 4098 participants (age 2-17 years, M=6.2, SD=3.44) from the Autism Treatment Network (ATN) consortium was divided into groups based on caregiver endorsement of current and previous diagnoses of depression or no current or previous diagnosis of depression. After controlling for age and ASD diagnosis, bivariate analysis of the data revealed significant differences in characteristics of the Depressed (N=135) and the Non-Depressed (N=3963) groups including: seizure and seizure disorders ($\chi^2 = 14.6, p< .001$), GI problems ($\chi^2 = 25.2, p< .001$), history of psychiatric disorders ($\chi^2 = .27.29, p< .001$), and self-injurious behavior and aggression ($\chi^2 = 18.63, p< .001$). The groups did not differ in reports of family history of depression and other psychiatric problems, eating problems, repetitive behavior, social deficits, or ADHD symptoms. These findings suggest that ASD subgroup(s) may exist with more complicated and numerous comorbidities. We also discuss implications for mechanisms, treatment, and screening depressive features in children and adolescents with ASD.
Music Training to Enhance Cognition in At-Risk Children

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Keywords: cognitive development, at-risk children, music, W.O. Smith Music School

Existing data suggest that music has beneficial effects on cognitive development, however research is limited. To our knowledge, no one has examined both academic and cognitive outcomes of a music training program in children. The W.O. Smith Music School provides individual music instruction to at-risk children from low-income households around Nashville. Despite positive feedback from teachers, parents, and students, the cognitive and school outcome of individual music lessons have not been examined systematically.

We sought to evaluate the effects of music training on cognitive and academic development of economically disadvantaged children by measuring cognitive functioning, academic grades, and behaviors at school, in those students enrolled in the Basic Musicianship class at three time-points: August and December 2013, and April 2014. Wait-listed students will also be tested at these time-points and serve as controls. Cognitive functions are assessed with CogState, a brief and computerized cognitive assessment program that can detect changes in psychomotor speed, visual attention and memory, executive function, and social cognition over time.

Baseline assessments with 36 students were completed in August 2013. 21 students were randomized to the Basic Musicianship class, and 15 students to the waitlist control group. The two groups were matched for the CogState scores at baseline. Follow-up data will be collected in December 2013 after the intervention group completes their Basic Musicianship class. Changes in cognitive performance from the baseline assessment will be compared across the two groups. Finally, in April 2014 we will compare the cognitive functioning in the two groups at a second follow-up, and will examine changes in academic grades and school behaviors from the previous semester for evidence of far transfer effects of the intervention.

Examining preliminary impact results, we will test to see if there are beneficial effects music training on a child’s cognitive development as defined by cognitive scores, academic performance, and on-task behavior. Outcome of the first follow-up results in December 2013 will be discussed.
Vocalizing while Watching Conducting-like Gestures: Kinematic Features of Conducting Drive Acoustic Features of Speech

Aysu Erdemir, Emelyne Bingham, Sara Beck and John Rieser

Keywords: conducting, gestures, psychoacoustics, music and movement, cross-modal

BACKGROUND: Conductors work to influence the tempo, dynamics and timbre of the singers and instrumentalists that they direct. How is it that musicians know how to map a conductor’s visual gestures onto features of the music they make? What spatio-kinematic features of the conductor’s movements influence what acoustic features of their music? This study presents an empirical investigation of the ways adults associate changes in visible motion with changes in acoustic parameters by asking people to view videotapes of a series of conducting-like gestures and to say the syllable /da/ while watching.

AIMS: The first aim was to investigate whether adults systematically vary the acoustic features of their utterances in response to the different motional features they observe visually. The second aim was to investigate the role of explicit instruction on the strength of cross-modal coupling, thereby to examine whether an automatic or controlled processing underlies the mapping.

METHOD: Non-musician college students were asked to view videotapes of four different hand gestures that differ in kinematic and dynamic properties, and to say the syllable /da/ simultaneously while they were audio-recorded. We manipulated the instruction so that it would entail no correspondence (n=20), a moderate correspondence (n=20), or a strong correspondence (n=20) between the gesture and sound. In the judgment task, we asked musically trained judges to (blindly) listen to the recordings and judge which of the 4 gestures the participant was observing while producing the sound. In order to bring out specific acoustic-kinematic associations, we performed a detailed acoustic analysis on the sound data by extracting duration (ms), amplitude (dB), fundamental frequency (Hz), pitch variability (Hz), and formant frequencies (F1, F2, and F3); and we performed a kinematic analysis on the gestures themselves after capturing the movements of the conductor using a high-resolution motion capture system.

RESULTS: The judgment task yielded significant hit rates. Psychoacoustic analysis revealed significant associations of the motion characteristics, namely time, energy, and space with acoustic characteristics of duration, amplitude and pitch levels, respectively. Kinematic analysis of the gestures showed associations of velocity with amplitude. Participants who were explicitly encouraged a matching strategy produced more pronounced variations. However, even the minimal instruction which involved no hint as to the underlying correspondence, resulted in some basic variations suggesting that cross-modal integration of (relatively simple) temporal and intensity features are result of an automatic processing, whereas pitch effects require more deliberate/controlled strategies.

CONCLUSION: The results demonstrate strong cross-modal links connecting vision to the auditory-motor system. We are exploring the learning and development of this link by testing professional musicians, children and infants.
Internal and External Bodily Perceptions in Schizophrenia

Channing J Cochran, Kim B Schauder, Carissa J Cascio, Sohee Park

Keywords: Schizophrenia, Multisensory Integration, Interoception, Proprioception,

BACKGROUND: Schizophrenia has long been hypothesized to be a self-disorder, characterized by an anomalous sense of the self and body. The ability to assess ones internal bodily state in relation to external environmental cues is imperative to daily social functioning. This integration of internal and external sensory cues is thought to play a central role in maintaining self-awareness. Past research suggests that proprioception is impaired in schizophrenia but less is known about interoception. In this study we compared two tasks assessing interoceptive and proprioceptive abilities in schizophrenia and healthy controls.

METHODS: Sixteen schizophrenia outpatients (SZ) and twenty-eight healthy controls (HC) participated in tasks assessing interoceptive and proprioceptive abilities. The interoceptive task involved assessing one's own heart beat. Participants were asked to focus on their heartbeat while attached to a sensor that measured their actual heartbeat. Two conditions were assessed. In the cognitive condition, participants reported how many times they thought their heart beat, and in the sensory condition, participants reported how many times they actually felt their heart beat. The proprioceptive ability was assessed with the Rubber Hand Illusion (RHI) task. Participants were asked to look at a fake rubber hand while their real hand was hidden inside a covered box. The experimenter brushed both the rubber hand and the participant's hidden hand with a paintbrush for 6 minutes. RHI can be elicited when the experimenter brushes the fake and real hand synchronously but not under asynchronous brushing. Subjective reports from a questionnaire and an objective measure of 'drift' toward the rubber hand were recorded after each block of brushing. Dissociative experiences and clinical symptoms were also assessed.

RESULTS: In the interoceptive task, HCs performed significantly better than SZs on estimating how many times their heart beat (p=.009, .038, .0003, and .003 for 25, 35, 45, and 100 seconds, respectively) but there were no significant differences in the sensory condition between groups. In the proprioceptive task (RHI task), there was a significant difference (p=.044) in drift between the two groups in the synchronous condition but not in the asynchronous condition. In SZs, there were significant correlations between RHI drift and increased incidence of out-of-body experiences, increased dissociative experiences, and more severe positive symptoms.

DISCUSSION: The results from the heart beat task indicate that SZ are less accurate at predicting their actual heartbeat when compared to HCs, suggesting impaired interoception. With respect to proprioception, SZ seemed to experience a weakened sense of self. These results could indicate impairments in multisensory integration of both internal and external bodily cues that may contribute to schizophrenic symptoms.
iTap on a Touchscreen: Age, Sex and Self-Regulation Affect Toddlers' Interaction and Learning

Colleen E. Russo, Charlotte A. Duncan, Georgene L. Troseth

Keywords: Touchscreen, Children, Technology, Educational apps, Learning

Young children's use of apps on touchscreens proliferating much faster than is research into the educational effectiveness of their use and the way that children interact with them. Whereas learning from children's television is a relatively passive process on the part of the child, learning from touchscreen apps requires the child's active contingent response. That is, the child must touch the screen in instructed ways in order to produce the intended educational experience. Failure to self-regulate and inhibit this desire to touch the screen may compromise the effectiveness of educational apps. In general, males have lower self-regulation than females, however in a review of published studies, we found no research about children's self-regulation and the use of touch screens. Therefore, our study investigated links between sex, age and self-regulation with children's interaction with and learning from touchscreen apps. Our main analysis, study 1A, focused on 27 children (mean age= 30 months). Children received two tests of self-regulation (Snack task and Sticker Delay task) and completed three different apps in order to measure their number of taps in various ways. Results demonstrate significant negative correlations between self-regulation and number of taps on the touchscreen (lower self regulation correlated with more taps). This finding, however, is moderated by the child's sex: females tap significantly less than males, and females have significantly higher self-regulation. Among these 27 two and three year old children, there were no affects of age. In order to further investigate age differences, study 1B included 14 additional children (ages 4-6) who completed one of the three tapping measures (which included novel word learning). This created three different age groups (means of 30 months, 52 months and 70 months). Results reveal a significant negative correlation between tapping during word learning instructions and the number of words learned, meaning those who tapped more during the instructions learned less words. This was moderated by age: there was a significant positive correlation between age and number of objects learned, and a significant negative correlation between age number of taps during the instruction slides. Trends in number of words learned based on the presentation order of the novel objects is also discussed.

Results demonstrate that to create quality educational experiences, app developers must carefully consider: how children will interact with the app's interface and content, how these interactions will affect learning, and how interaction and learning may differ between groups of children (e.g. groups based on age and sex). Aggregate data from parental surveys of 70 children are reported, providing interesting insight into children's use of touchscreens.
Purpose: The purpose of this study was to empirically assess whether preschool-age children who stutter (CWS)' emotional diathesis (vulnerability), emotional stress, and their interaction are associated with their stuttering frequency and whether those associations are mediated by sympathetic arousal. 

Method: Participants were 60 preschool-age CWS. Each participant was exposed to relatively neutral (i.e., baseline), positive and negative emotion-inducing child video clips and then performed age appropriate narrative tasks. Measurement of participants' emotional diatheses (e.g., emotional reactivity) were based on parents' report and their stuttered disfluencies were measured during a narrative after viewing each baseline, positive and negative video clip. Participants' sympathetic arousal, as indexed by tonic skin conductance level, was measured during a 4 min. period of observation of each baseline, positive and negative video clip.

Results: It is speculated that preschool-age CWS' emotional diathesis, emotional stress, as well as their interaction will affect frequency of stuttered disfluencies. It is also speculated that such relations will be mediated by sympathetic arousal.

Conclusions: Findings are expected to shed light on how children’s emotional diathesis and emotional stress they experience are independently as well as jointly be associated with childhood stuttering.
Multiple-Meaning Word Learning: An Intervention Study

Dana Kan, Stephen Camarata, Megan Roberts, Anne Marie Tharpe

Keywords: vocabulary, word-learning, intervention,

Words with multiple meanings (e.g., "bat" can mean a flying mammal or a piece of baseball equipment) are particularly challenging to learn, but are crucial for listening and reading comprehension. This study compared two interventions that targeted the acquisition of multiple-meaning words. The "jointpresentation" method taught two meanings of a word at the same time; the "separate-presentation" method taught a second meaning only after a first meaning had been learned. An adapted alternating treatments design was used to test for a functional relation in 4 typically-developing preschoolers.

Eighteen words (i.e., 36 meanings) were divided into 3 groups: joint-presentation, separate presentation, and control words. Each session began with a probe, followed by the intervention. Sessions lasted approximately 15 minutes and were conducted 3 times per week. Acquisition of the words was assessed by asking children to name the word when shown an image of the meaning. Three of the four children learned all the target words in both conditions. Three of the four children reached criterion in the separate-presentation condition prior to the joint-presentation condition. Future directions include implementing the procedures with young children with hearing loss.
Examining the Effects of Jasper and Enhanced Milieu Teaching on Repetitive Behaviors and Scripted Language

Elizabeth Fuller, Jennifer Nietfeld, Lauren Hampton, Ann Kaiser, Connie Kasari

Keywords: Autism, Repetitive Behaviors, Language, Early Intervention,

Restricted and repetitive behaviors, interests, and activities (RRBs) are one of two core diagnostic features of autism spectrum disorder (American Psychiatric Association, 2013). RRBs define a broad category of behaviors, including motor stereotypies, unusual sensory preoccupations, and echolalia. RRBs have been shown to interfere with child learning (Koegel & Covert, 1972) and have been the focus of a broad range of behavioral interventions (Rapp & Vollmer, 2005). The current study examined the extent to which RRBs change over the course of an intervention targeting social attention, play and spoken language, and the relationship between scripted language and social communicative utterances.

Objectives: 1) What is the relationship between parent-reported RRBs, the repetitive behavior score on the ADOS, and observed measures of RRBs? 2) Do these measures change over the course of intervention? 3) Over the course of intervention, does observed repetitive behavior decrease as language increases?

Methods: Twenty minimally verbal (less than 20 words) children diagnosed with ASD between the ages of 4.5 and 8 years old participated (16 males, mean age 6.39). The intervention used the strategies associated with JASPER/Enhanced Milieu Teaching (Kasari et al, submitted) to teach joint attention, nonverbal and verbal requests, and comments. Data were selected from the pre and post intervention assessments, approximately 3 months apart. The repetitive behavior subscale of the ADOS was measured pre-intervention, and parent-reported Repetitive Behavior Scale (RBS), social communicative utterances (SCU), and scripted language were measured pre- and post-intervention.

Results: Results show that there was not a significant correlation between ADOS repetitive behavior subscale and pretest RBS scores (r=.202, p=.436), or between ADOS repetitive behavior subscale and scripted language on the language sample at pretest (r=.123, p=.606). Over the course of intervention, while total social communicative utterance did show significant changes (t = -2.3918, p = 0.02727), RBS did not show significant changes from pretest to posttest (t =0.414, p = 0.684). RBS remained low pre- and post-test (pre test mean=30.11, sd=20.27, post test mean=34.15, sd=24.23). Decreases in scripted language only approached significance (t = 1.7147, p= 0.1027). Changes in social communicative utterances were not significantly related to changes in scripted language over the course of intervention (r=.276 p=.239).

Conclusions: There are several possible explanations for the nonsignificant findings. First parents rated their children as having low levels of RBS although observations during the ADOS suggested moderately high levels of repetitive behavior. Second, some children had extremely low rates of any language behavior during the language sample session, including both social communicative utterances and scripted language. These factors, combined with the small sample size, may have affected the outcomes. To further examine the functional relationship between behavior and language during the sessions, we are coding all repetitive behaviors, during the first two intervention sessions compared to the final two intervention sessions. We hypothesize that the inclusion of motor stereotypes as well as verbal scripts will provide a more representative data set to answer to the question of correlation between changes in observed RRBs and language over the course of intervention.
Predictors of word reading development: The role of dynamic assessment

Eunsoo Cho; Donald L. Compton

Keywords: word reading, assessment

In contrast to conventional static assessments measuring what students have learned, dynamic assessments (DA) measure how well students can learn by embedding instruction within the test and quantifying students’ response to such instruction. Empirical evidence of predictive validity suggests DA has some added value in predicting students who will be at risk for learning difficulties beyond other predictors of reading. However, incremental validity of DA for explaining later word reading skills when controlling for the current level of the skill being predicted has rarely been investigated. This study investigated whether DA can predict students’ word reading development beyond that which can be explained by current level of word reading skill as well as other predictors of reading (phonological awareness; PA, rapid letter naming; RLN, and paired associate learning; PAL). If DA measures student’s potential to learn rather that what has already been learned, DA should predict later word reading controlling for current level of that reading skill. In the fall of first grade, 108 students were given DA of decoding, PA, RLN, PAL, and standardized word reading assessments. These word reading assessments were given again at the end of first grade. In the hierarchical regression model predicting spring word reading, fall word reading were entered first, then other predictors of reading, followed by DA. Overall model was significant, F (1, 102) = 141.22, and DA was a significant predictor of later untimed word reading, b=.45, t=2.07, along with fall word reading, PA, RLN. The model with DA significantly improved R2 by .005. However, DA failed to show incremental validity in predicting timed word reading. The results suggest that DA is a measure of students’ potential in learning how to read and DA could lend us important source of individual differences in explaining students’ word reading growth.
Understanding trajectories of diurnal rhythm of cortisol in children with autism based on psychological and behavioral profiles

Gloria T Han, Andrew J Tomarken, Blythe A Corbett

Keywords: Autism, Diurnal Cortisol, Stress, Sensory Sensitivity

Background: Individuals with autism spectrum disorders (ASD) are characterized by marked impairments in social interaction and communication, stereotypic repetitive behaviors, and difficulties responding to changes throughout the day. Furthermore, children with ASD also present significant heterogeneity in their profiles of stress responsivity. Previous studies investigating diurnal rhythm of cortisol have shown notable variability and dysregulation of cortisol throughout the day in children with ASD compared to typically developing (TYP) children. Moreover, findings suggest that sensory sensitivity may be a moderator of reactivity to daily stress, though few studies provide a comprehensive analysis of diurnal cortisol in children with ASDs.

Objective: Extending previous findings, this study aimed to assess the stability of the diurnal cortisol profile in ASD and TYP children, and then sought to clarify the between- and within-group differences through consideration of time-of-day differences, behavioral, and psychological factors as potential covariates of cortisol regulation.

Methods: The study sample consisted of 64 unmedicated, prepubertal children between 7 and 12 years old, 36 with ASD and 28 typically developing children. Salivary cortisol was collected for three diurnal cycles, consisting of four samples per day (T1: waking, T2: 30-minutes post-waking, T3: afternoon, T4: 30-minutes before bedtime), for a total of 12 samples per child. All participants completed a battery of neuropsychological tests, including measures of intelligence (IQ) and parent-report measures of sensory sensitivity, stress sensitivity, and adaptability to change. Data were analyzed using a piecewise linear mixed effects model with the cortisol awakening response (T2-T1) separated out from the linear decline of cortisol levels from the awakening response until the end of the day (T2 to T4).

Results: Preliminary results indicate that the two groups differ in steepness of the linear decline from T2 (30-minutes post-waking) to T4 (30-minutes before bedtime), with individuals with ASD having a flattened slope compared to the TYP group and elevated evening cortisol. Furthermore, there is a dampening effect of peak cortisol and linear decline in the ASD group from Day 1 to Day 3. In this sample, age, IQ, and sex do not significantly affect diurnal cortisol trajectories. However, scores on sensory and stress sensitivity, time of awakening, and adaptability to change throughout the day (and their interactive effects) are still to be explored to elucidate between- and within-group differences of diurnal rhythm.

Conclusion: Findings support emerging literature emphasizing the identification of specific subgroups of children with ASD, such as those with increased sensory sensitivity, and how cortisol regulation is moderated in terms of differential individual profiles. The findings support a complex interplay between physiological and behavioral stress and sensory sensitivity.
Sympathetic Arousal During Picture-Naming of Preschool-Age Children Who Stutter

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Keywords: Stuttering, Children, Autonomic Nervous System, Sympathetic

Purpose: The purpose of the current study was to investigate sympathetic arousal of preschool-age children associated with a picture-naming task under instructions to name pictures as rapidly as possible.

Method: Thirty-five preschool-age children who stutter (CWS) and 39 preschool-age children who do not stutter (CWNS) served as participants. Dependent measures consisted of tonic skin conductance during a pre-task baseline, a picture-naming task, and post-picture-naming task condition.

Results: Findings indicated that, when chronological age is not taken into account, there was no between-group difference in tonic skin conductance level. When age was taken into account, however, there was a significant talker group x age group interaction, with follow-up analyses indicating that 3-year-old preschool-age CWS exhibited significantly higher sympathetic arousal than their CWNS peers, whereas the 4-year-old CWS exhibited significantly lower sympathetic arousal than their CWNS peers during picture-naming task.

Conclusions: Present physiological findings were taken to be consistent with non-physiological studies indicating an association between emotional processes and childhood stuttering; however, this association, at least for physiological indexes of emotional arousal during picture naming, was moderated by children's chronological age.
A Statewide Examination of Training Needs Related to Educating Students with Autism

Heartley B. Huber, Matthew E. Brock, Erik W. Carter

Keywords: autism, evidence-based practices, professional development

Given the recent push to ensure the use of evidence-based practices in schools, the training and professional development of teachers on these high-impact practices is a vital issue. Providing professional development opportunities that meet the needs of teachers, as well as offering trainings in which teachers are likely to participate is an ongoing challenge for many schools and districts. Understanding the training needs of teachers and their interest in participating in trainings on these topics can help ensure states, districts, and schools offer professional development opportunities in ways that maximize impact and efficiency.

We partnered with the Tennessee Treatment and Research Institute for Autism Spectrum Disorders (TRIAD) to survey special education supervisors, school-based special education administrators and supervisors, and special education teachers who work with students with ASD in across the state of Tennessee. Participants included 274 teachers and 172 administrators from geographically and economically diverse schools across the entire state. This survey focused on training needs related to ASD, specifically (1) the degree to which teachers were confident implementing evidence-based interventions and educational practices addressing topics related to ASD, (2) their likelihood to access training on various evidence-based practices, and (3) their preference for various avenues of training (e.g., workshops, conferences, webinars, etc.). The survey included questions regarding teachers' proficiency in implementation and desire for training in 24 evidence-based intervention practices for students with ASD, identified by the National Professional Development Center on Autism Spectrum Disorders (Odom, Collet-Klingenberg, Rogers, & Hatton, 2010). An additional 12 areas of special education practice were identified by TRIAD staff and the authors of this study based on our experience in teaching and professional development related to ASD.

We found that nearly half of all teachers of students with ASD were not at all confident (23.7%) or only a little confident (25.9%) in their implementation of evidence-based practices for students with ASD. Yet, more than half of administrators were a little (24.5%) or somewhat confident (33.0%) in their staff's ability to implement evidence-based practices. While both teachers and administrators indicated a need for training, for teachers, lower ratings of teacher confidence were not associated with higher interest in training (e.g., negative correlation) at a statistically significant level. Lower confidence among administrators was associated with higher interest in training for 10 of the practices. Finally, descriptive differences in interest in accessing various avenues of training were found based on geographical region.
Do language and fluid reasoning predict performance on pre-literacy tasks?

Hope S Lancaster, Stephen Camarata

Keywords: children, language, cognitive, literacy

Introduction: Children with language impairments (LI) are at a higher risk than their typical peers for reading deficits (Bishop & Adams, 1990; Catts, Hu, Larrivee, & Swank, 1994). Research has indicated that children with LI show deficits in pre-literacy (PL) skills, such as phonological awareness (Larrivee & Catts, 1999). One possible reason that children with LI have deficits in PL skills might be related to other cognitive skills (Catts, Fey, Zhang, & Tomblin, 1999), in particular their ability to manipulate information (fluid reason, Gf). Gf ability can be tested using both high and low language demands; this means that children with LI might show a different relationship when predicating PL performance based on whether a test of Gf had high or low language demands. The purpose of this study was to examine how Gf and language interact to predict performance on pre-literacy tasks. The research questions were: (a) is there a difference in the strength of predicative power when considering the amount of language demand for a measure of fluid reasoning, and (b) is the predictive pattern the same for children with typical language, specific language impairment (SLI), and nonspecific language impairment (NLI)

Methods: This study used the publically shared EpiSLI database (PI: Tomblin). The database contains 1935 subjects (typical = 1429, SLI = 277, NLI = 229). The independent variables used in this study were Word-Sound Deletion and Letter-Word Identification. The dependent variables were a language composite created by Tomblin, and Block Design and Picture Completion from the WPPSI-R (Weschler, 1989). Hierarchal regression analyses were completed; both main effects and interactions were explored.

Results: Analyses for predicting Word-Sound Deletion were significant in all groups. After controlling for language Gf tasks did predict performance on Word-Sound Deletion; although the pattern for main effects and interactions differed for each group. Children with SLI had a significant interaction between language and Picture Completion (high language Gf task). Analyses for predicting Letter-Word Identification performance were not as strong as for Word-Sound Deletion. In the typical and SLI samples, language was an important predictor, this was not true in the NLI sample. For the NLI sample, Picture Completion was the strongest predictor.

Discussion: Gf is important for predicting performance on PL tasks, especially for the two LI samples. In examining the two LI samples, the patterns for predicting performance suggest that children with SLI and children with NLI have different relationships between PL and Gf. The implication for these findings is that there are differences in the strengths and needs for children with SLI and children with NLI.
Flexible Training with Tools Supports Transfer in Infancy

Jane Hirtle, Amy Needham

Keywords: Cognitive Development, Infancy, Tool Use

Previous research demonstrated that infants can be trained to use a novel tool in either a strict manner using a single grasp consistently, or in a flexible manner using multiple grasps (Barrett, Davis, & Needham, 2007). Following such training, infants performed best on novel tasks that required the same grasp they had been trained to use. The current study expands these findings by exploring how strict versus flexible training influences transfer of tool use knowledge to novel tool exemplars.

14.5- to 18.5-month-old infants received either strict or flexible training with an unfamiliar tool and then were tested on their ability to use that same trained tool, a novel but similar tool, and a novel but different tool to solve two test tasks. Despite their perceptual dissimilarities, all tools provided the same functional affordances. Further, each test task required a different grasp for its solution, and infants observed only the trained tool used in demonstrations of the tasks. Thus, in order to succeed with each tool in both tasks, an infant would have to transfer their knowledge of the trained tool to each novel tool. Prior studies showed that with experience, infants transfer problem solving knowledge to novel tools (Brown, 1990) and anticipate multiple functions for a single tool (Paulus, Hunnius, & Bekkering, 2011). We thus predicted that infants who received flexible training would be better able to transfer learning from the trained tool to the other tools than would infants who received strict training.

Preliminary results support these predictions. A two-way mixed ANOVA with tool as a within-subjects factor (3 levels) and training group (2 levels) as a between-subjects factor revealed a significant main effect of tool (F = 5.126, p = .011). A main effect of training group and an interaction effect between tool and training group both trend toward significance (F = 4.326, p = .052 and F = 2.287, p = .116 respectively). Effects will likely strengthen as more data is collected (current N = 20).

Overall, infants were significantly less successful on the test tasks with the similar and different tools rather than with the trained tool. However, this decline was precipitous in strictly trained infants while flexibly trained infants were about equally successful with all tools. Indeed, a follow-up two-way mixed ANOVA examining performance on only the similar and different tools (2 levels within-subjects factor, 2 levels between-subjects factor) revealed a main effect of training group (F = 7.22, p = .015). Results will be further discussed in terms of tool use development in general and early creative problem-solving ability.
Poster: 73 Session: 1

Presenter: Jasia Mahdi (jasia.mahdi@vanderbilt.edu) Lab PI: Nirupama Madduri

The Influence of Islamic Values on how Parents Face and Cope with a Family Diagnosis of Autism

Jasia Mahdi

Keywords: Islam and Autism

In traditionally Islamic countries, Autism Spectrum Disorder is often ignored and misunderstood. Accordingly, children with autism in these societies are sometimes neglected and ostracized despite the Islamic precedent that promotes the acceptance and respect of these children. Through a series of interviews we examined the specific influence of Islamic values on the way the diagnosis of autism is regarded and how it influences the way families perceive, treat, raise, and educate their children. Additionally, we looked at the influence of Islamic values on the way children are integrated into their families, social and religious circles, and academic community. In the course of our study we found that even though faith served as a source of strength for parents with children with autism and was emboldened upon taking care of their children, these families were often isolated from their religious circles and extended families and met great intolerance as well as a lack of proper understanding, acceptance, and support from these communities.
Language Assessment of Students with Emotional Disturbance: An Analysis of Teacher Concordance

Jason Chow

Keywords: Behavior, Language, Emotional Disturbance, Teacher Ratings, Concordance

The co-occurrence of language and behavioral problems in school-age children and youth has been well documented in research literature; yet the extent to which practitioners are aware of this connection is unknown. Although language impairment (LI) is seldom formally identified in students with primary educational labels of emotional disturbance (ED), it is possible that teachers are aware of student's linguistic strengths and limitations in the absence of formal assessments. Conversely, it is possible that a range of subtle language deficits are overlooked in these students due to their highly visible problem behavior. It is important for teachers to consider that academic and social demands present in school settings are mediated by language, and therefore may present additional challenges for students with ED and low language skills.

The current study relates to the theme overall conference theme because identifying and supporting students with low language skills may be a critical element in prevention and intervention on behalf of students with challenging behaviors. We will report analyses of teacher ratings and student performance on standardized language assessments in a sample of school-age students with primary educational labels of emotional disturbance. Teachers will complete the Children's Communication Checklist-2 (CCC-2; Bishop, 2006), a standardized rating scale developed to identify children with pragmatic language impairment, specific language impairment, and children who may require further assessment relative to autism spectrum disorders. Students will complete the Comprehensive Assessment of Spoken Language (CASL; Carrow-Woolfolk, 1999), a well-known standardized measure that provides receptive, expressive, pragmatic, and meta-linguistic index scores. Descriptive statistics will be presented, as well as the concordance of teacher ratings and student performance. We also will compare and analyze the results relative to types of student problem behavior using the Teacher's Report Form (TRF; Achenbach & Rescorla, 2001).
Relations between Parents' and Children's Positive and Negative Affect and Depression

Jennifer Bauman, Elizabeth McCauley, Guy Diamond, Kelly Schloredt, Judy Garber

Keywords: Depression, Positive Affect, Parents, Adolescents, Negative Affect

The current prospective study examined the relations between positive and negative affect and depression in children and parents. Participants were 226 parent-child dyads. Children (53% female) were 7-17 years old (M=12.53, SD=2.33), 70% Caucasian, 21% African American, 4% multi-race, and <1% Asian. Positive and negative affect and depressive symptoms were assessed in both parents and children at two time points that were four months apart. Children completed the Child Depression Inventory (CDI; Kovacs, 1985) and the Positive and Negative Affect Scale (PANAS; Watson, Clark & Tellegen, 1988); parents completed the Beck Depression Inventory (BDI; Beck et al., 1961) and PANAS. Additionally, clinicians interviewed parents about their depressive symptoms in the last week using the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960).

First, we conducted regression analyses to examine the relations between affect and depressive symptoms in children. Using residualized change scores, we found that increases in children's depressive symptoms were associated with decreases in PA and increases in NA over time (p's<0.01). We also examined the reverse direction of these relations and found that increases in PA predicted decreases in CDI scores (p<0.01), and increases in NA predicted increases in CDI scores (p<0.01).

Analysis of the relation between parents' affect and depressive symptoms yielded similar results. Increases in parents' depressive symptoms were associated with decreases in PA (p<0.01) and increases in NA (p<0.01) over time. The reverse relations also were significant. Increases in PA predicted decreases in depressive symptoms (p<0.01), and increases in NA predicted increases in depressive symptoms (p<0.01).

We next conducted separate regression analyses to explore the association between parents' and children's depressive symptoms and affect. Increases in parents' depressive symptoms significantly predicted decreases in children's PA (p<0.01), and showed a nonsignificant trend to changes in children's NA (p=.09). Increases in parent's PA significantly predicted increases in children's PA, but was not significantly related to changes in children's NA. Finally, changes in parent's NA was not significantly related to changes in children's PA, NA, or depressive symptoms.

These results are consistent with the literature showing that in both adults (Watson et al., 1988), and children (Lonigan et al., 1999) the association of depressive symptoms with NA is positive and with PA is negative. These prospective findings further advance our understanding of the relations among these constructs across time. Another interesting finding was that changes in parents' depressive symptoms and affect significantly predicted changes in children's affect, particularly PA. These results highlight that interventions aimed at reducing parents' depression should also examine the impact on children's positive affect. Future studies should explore possible mechanisms underlying the relation between changes in parents' and children's depression and affect. To what extent are these relations bidirectional or due to some shared third variable (e.g., stress, genes)?
Co-Occurring Child Maltreatment and Adult Social Anxiety: A Cumulative Perspective on Assessment

Jessica E. Thurmond

Keywords: child maltreatment, social anxiety, assessment,

Physical and sexual abuse has been shown to result in internalizing behaviors such as posttraumatic stress disorder, anxiety and depression (Buckner, Bearslee and Bassuk, 2004; Feiring, Simon & Cleland, 2007). Research conducted in 2003 found that exposure to co-occurring forms of child maltreatment resulted in significantly higher trauma symptomology in an undergraduate sample (Clemmons, DeLillo, Martinez, DeGue & Jeffcott, 2003). The primary objective of the present study was to see if these findings would generalize to a different sample of undergraduates by testing for group differences in trauma symptoms as well as social anxiety among adult participants subjected to co-occurring forms of maltreatment (18%), one form of maltreatment (34%), and no maltreatment during childhood (48%). We hypothesized that (H1/H2) mean trauma and social anxiety scores of participants subjected to two forms of childhood maltreatment would be significantly higher than those subjected to one or no forms of maltreatment, and (H3) there would be no significant differences between those subjected to one and no forms of maltreatment. Self-report questionnaires were administered to 440 undergraduate students (87 men, 351 women, 2 not reporting sex, M= 21.9 years, SD= 6.6) through anonymous online surveys. Measures included a demographic questionnaire, the Trauma Symptom Checklist-40 (TSC-40), the Liebowitz Social Anxiety Scale and the Sexual and Physical Abuse Questionnaire (SPAQ). This investigation employed two, one-way, between-subjects analysis of variance (ANOVA). Results indicated significantly greater trauma symptomatology at the p < .05 level in participants who experienced co-occurring childhood maltreatment in comparison to participants reporting one or no forms of maltreatment, F (2,189.5) = 4.4, p < .01. Results of the second ANOVA also indicated significantly higher adult social anxiety at the p < .05 level in participants who experienced co-occurring maltreatment versus those who reported one or no forms of maltreatment, F (2,435) = 9.1, p < .01. In a secondary analysis, participants reporting only physical abuse (n = 50), only sexual abuse (n = 51), and both forms of abuse (n = 38) were analyzed separately to assess whether one form of abuse could be overshadowing the effect of the other when both were present. Results of the ANOVA showed no significant difference between physical and sexual abuse for both social anxiety and trauma symptomatology. The findings supported all three hypotheses and suggest that varying levels of maltreatment may present a hierarchical method for assessing the cumulative influence of childhood trauma on adult outcomes. Future research should aim to explore whether this linear increase in symptomatology continues to be pervasive when assessing multiple layers of maltreatment.
Is there an emotion paradox in schizophrenia: A multi-channel psychophysiological investigation

Joel S Peterman, Esubalew T Bekele, Dayi Bian, Nilanjian Sarkar, Sohee Park

Keywords: Emotion Perception, Psychophysiology, Schizophrenia

Previous findings in the area of emotional functioning in schizophrenia have alluded to the presence of an emotion paradox. While individuals with schizophrenia self-report experiencing congruent emotions during evocative events, the psychophysiological findings have indicated either hyper-responses or hypo-responses to these events when compared to healthy controls. Furthermore, these previous studies have only used a small number of channels (e.g. electromyographic activity, galvanic skin response) in any given investigation. The present study attempts to elucidate this paradox by assessing five psychophysiological channels during a baseline period of the participant sitting calmly in the room and then during performance on an emotion recognition task. Post-task processing of the psychophysiological signals provided 41 features that were entered into a principal components analysis. These features were reduced to 24 components that were then subjected to K-Means clustering. By entering the components from the baseline condition and during the emotion recognition task, we were able to determine whether there was dissociable psychophysiological response during task performance compared to baseline. Furthermore, we are able to determine whether the patient group's psychophysiological signals dissociate to the same degree as healthy controls. This study provides a data driven approach to understanding the potential dissociation between self-report and physiological response in individuals with schizophrenia when experiencing emotions.
Assessing Enhanced Emotional Empathy in Williams Syndrome through Prosody Analysis

Jordan L Plaxico, Tricia Thornton-Wells, Elizabeth Roof, Matthew Snodgrass, Sohee Park

Keywords: Williams Syndrome, Empathy, Prosody, 

Williams Syndrome (WS) is a neurodevelopmental disorder caused by the deletion of ~25 genes on chromosome 7 that causes specific heart defects, "elfin"-like facial features, and hypercalcemia (McKusick, 1988). Individuals with WS have a specific cognitive profile that involves mild to moderate intellectual disability with pronounced deficits in visuospatial abilities, along with normal-to strengthened verbal abilities and short-term memory (Howlin et al, 1998, Mervis et al., 2000, Eckert et al., 2006). Behaviorally, WS individuals show enhanced emotional reactivity to music (Don et al., 1999; Hopyan et al., 2001), are highly sociable and empathic (Jarvinen-Pasley et al., 2008), but also impaired in social judgment (Einfeld et al., 1997; Gosch and Pankau, 1997) which can lead to possibly harmful situations such as approaching and trusting strangers.

It is important to examine empathic processes of people with WS, to understand the impact that enhanced empathy has on social interactions. Empathy is defined as the ability to share another person's emotions and feelings and is often assessed using self-report questionnaire in the general population. However, self-report measures may not be sufficiently reliable for assessing empathy in WS and other conditions that are also associated with cognitive impairments.

The major goals of this study was to develop an objective measure to assess empathic processes in individuals with WS and compare them to typically developing controls using speech samples extracted from naturalistic social interactions. Specifically we examined acoustic patterns of speech from a 'knee bumping task' in which a confederate bumps his knee in front of a participant and displays signs of distress in order to elicit speech from the participant. Speech is recorded and later analyzed using Praat software to extract the maximum and minimum fundamental pitch frequencies during the interaction. The difference in the pitch range provides an estimate of prosody. A control speech sample is also collected to obtain the baseline pitch range.

We hypothesized that participants with WS will have a higher percent increase from baseline in pitch during their spontaneous speech response while interacting with someone who appears to be in pain than typically developing controls. A higher percent increase in pitch corresponds to a more emotionally charged speech response towards the person in pain.

The WS data were obtained from a previously studied sample from the ACM Lifting Lives Music Camp at the Vanderbilt Kennedy Center. Healthy control data were collected from the psychology subject pool. The outcome of the prosody speech analyses will be presented at the Science Day.
Low levels of agreement between parents' and children's reports about parenting are noteworthy (Maurizi, Gershoff, & Aber, 2012). What contributes to this discordance is not well understood (De Los Reyes & Kazdin, 2005; Ehrlich, Cassidy, Dykas, & 2011). The present study examined children's perceived attachment and parents' depression as predictors of the discrepancy in parents' and children's reports about parenting and relationship quality.

Participants were 226 parent-child dyads. Children (53% female) were 7-17 years old (M=12.53, SD=2.33), 70% Caucasian, 21% African American, 4% multi-race, and < 1% Asian. Children completed measures about their parents' levels of acceptance, psychological control, and monitoring (Children's Report of Parent Behavior Inventory; CRPBI) and the extent of conflict with the parent (Conflict Behavior Questionnaire; CBQ). Parents (76% female) completed the same measures regarding their relationship with their child. Parent-child discrepancy scores for each variable were calculated by standardizing the scores and subtracting the child's report from the parent's report. Positive scores indicated parental over-reporting and negative scores indicated parental under-reporting relative to the child's report. Children also completed measures about their attachment to their parent (Inventory of Peer and Parent Attachment; IPPA) and about their depressive symptoms (Children's Depression Inventory; CDI); parents completed a measure of their depressive symptoms (Beck Depression Inventory; BDI).

Linear regression analyses examined attachment and parental depression as predictors of the parent-child discrepancy scores regarding the extent of parental acceptance, psychological control, monitoring, and conflict, controlling for children's depressive symptoms, age, and sex. Attachment significantly predicted discrepancy in parent-child reports of parental acceptance (B=-.41, p=<.001), psychological control (B=.30, p=.001), monitoring (B=.03, p=.001), and conflict (B=.31, p=<.001). Parental depression significantly predicted discrepancy in parent-child reports of parental acceptance (B=-.19, p=.003) and conflict (B-.29, p=.001).

These cross-sectional results indicate that relative to their parents' reports, more securely attached adolescents reported higher levels of parental acceptance, lower levels of psychological control, and higher levels of monitoring as well as lower levels of conflict in their relationship with their parent as compared to their parents' reports about these parenting behaviors. Second, parents with higher levels of depressive symptoms tended to report lower levels of acceptance and higher levels of conflict in their relationship relative to their child's report. Thus, children's reported attachment to their parent and parents' level of depressive symptoms may partially explain discrepancies in parent-child reports of parenting. Therefore, differences between informants likely reflect their unique perspectives and should not be dismissed simply as measurement error. Longitudinal studies are needed to examine the relation of these predictors to parent-child discrepancy scores across time. Implications for the assessment of the family environment in families with a depressed parent will be discussed.
The Effects of Enhanced Milieu Teaching (EMT) + Sign on Parent Use of EMT Strategies and Sign Language

Kelly S. Windsor, Ann P. Kaiser, Courtney A. Wright

Keywords: Language, Intervention, Down Syndrome, ,

Children with Down Syndrome are characterized by deficits in their overall rate of verbal communication, the complexity and length of their utterances, their pragmatic skills in social interactions, and the quality of their speech (Roberts, Price & Malkin, 2007). Previous research on the use of Enhanced Milieu Teaching (EMT) has indicated that following intervention, children with Down syndrome show comparable progress to that of children with other intellectual disabilities on standardized testing, but make less progress in number of different words and in average length of utterances (Windsor, Kaiser, & Roberts, 2013). Wright (2013) conducted a pilot study in which a therapist implemented EMT + Sign language with four young children with Down syndrome and later taught EMT + Sign to their parents, yielding positive results for parent use of strategies and child use of language. The current study extended Wright’s work by conducting parent intervention concurrent with therapist intervention and implementing strategies across multiple routines.

Research questions included:
1) Does parent training in EMT + Sign result in increased parent use of matched turns, expansions, time delay strategies, and prompting strategies?
2) Does parent training in EMT + Sign result in increased parent use of signed language?
3) Does child use of signed or spoken language increase following intervention?

Participants were two mothers and their young children with Down syndrome. The child participants were two females 22 months of age and 18 months of age at entry into the study. The study design was a multiple baseline within and across parent participants. Each dyad participated in baseline observations of play and other routines. Play sessions were videotaped and coded. When child communication and parent use of strategies were stable, the first dyad began intervention. During each intervention session, the therapist 1) taught the current strategy, 2) modeled strategies in play with the child, 3) coached the parent in practicing the strategies, and 4) reflected with the parent on the session. EMT + Sign strategies were introduced sequentially across parent sessions (Notice & Respond, Model & Expand, Time Delay, Prompting). When the first parent showed progress in use of the first set of strategies, the second dyad began intervention. After a parent reached criterion on one strategy, the next strategy was introduced.

Both parents learned and used EMT strategies to criterion. Both parents signed more than 75% of words used in final intervention sessions. Child performance during coded session time was variable. Both parents reported that children used more signs and words following the intervention. Results and implications of this study will be discussed.
Social isolation, loneliness and delusions in schizophrenia; a test of the social deafferentiation hypothesis

Laura L. Hieber, Taylor L. Benson, Sohee Park

Keywords: schizophrenia, loneliness, delusions, social deafferentiation,

Schizophrenia is characterized by social withdrawal, as well as hallucinations and delusions that are almost always social and emotional in nature. However, the relationship between these symptoms has not yet been causally determined. The social deafferentiation hypothesis (Hoffman, 2007) has been proposed to explain the emergence of hallucinations, delusions and social impairments in schizophrenia; analogous to hallucinations induced by sensory deprivation, high levels of social isolation in vulnerable individuals trigger over-activation of the social brain network to construct social meaning where it is absent in reality. Therefore, it is likely that social isolation and loneliness could lead to increased positive symptomatology in the schizophrenia-spectrum. Loneliness is a chronic, gnawing condition that induces distress and impedes life satisfaction and function. Previous work has posited a 'cognitive discrepancy' model whereby an incongruity between actual versus desired level of social involvement contributes to feelings of loneliness, suggesting that it is not necessarily the amount of social involvement, but rather a dissatisfaction with the amount that causes this distress. Although it is largely assumed that social anhedonia in individuals with schizophrenia indicates an absence of desire for interaction and accounts for social withdrawal, this has not been systematically tested. We sought to determine the contributions of loneliness to positive syndrome in individuals with schizophrenia (SZ) and matched healthy controls (HC) by administering the Peters et al. Delusions Inventory (PDI) and UCLA Loneliness Scale to both groups of participants. Symptom severity in SZ was assessed by the Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms, and Brief Psychiatric Rating Scale (BPRS). We hypothesized that increased loneliness would be associated with increased positive symptoms, particularly delusions, in SZ and with increased schizotypy in HC. Findings reveal that in fact, SZ experience higher levels of loneliness than HC, contradicting traditional accounts of social anhedonia in schizophrenia. Increased loneliness corresponded to higher levels of paranoia and symptomatic distress in SZ. This work demonstrates that SZ desire social interaction and feel cognitive discrepancy as manifested by loneliness. We also corroborate Hoffman's hypothesis that social deprivation may lead to creation of social meaning where there is none, and highlights the potential severe consequences of loneliness and social isolation in individuals predisposed to psychosis. Moreover, reduced capacity to socialize in SZ and the stigmatic nature of the illness could further prevent normalization of social interactions, thereby impeding prospective remediation efforts. Future work will focus on social isolation intervention efforts to diminish distressing positive symptoms in schizophrenia.
Multidimensional Assessment of Empathy in Children with ASD

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Keywords: ASD, Empathy

Background: Research suggests that empathy consists of multiple constructs. Cognitive empathy (CE) is the capacity to infer others' mental states. Affective/emotional empathy (EE) is the observer's emotional response to another person's emotional state. Previous studies examining CE and EE in autism spectrum disorders (ASD) report impaired CE but intact EE (Rogers et al. 2007). Many previous studies measured either CE or EE and relied on self-report of EE. To address these concerns, Dziobek et al. (2008) developed the Multifaceted Empathy Test (MET) that simultaneously measures CE and EE in a direct (sympathy) and indirect (arousal) manner. Their results replicated previous studies showing impaired CE but intact EE in adults with ASD. However, there are no published reports utilizing this multidimensional paradigm in children with ASD.

Objectives: We aimed to simultaneously measure CE and EE in children with ASD using a modified version of the MET, the Multifaceted Empathy Test-Juvenile (MET-J: Poustka et al., 2010).

Methods: 19 children with ASD and 17 typically developing (TD) children, ages of 7-16, participated. Participants viewed photographs of people in emotionally charged situations and were asked to infer the person's emotion by choosing from a list of four adjectives (CE). As an indirect measure of EE, participants were asked to rate their arousal in response to each picture using a visual-analog scale (Lang et al. 1997). Lastly, as a direct measure of EE, participants rated how much they sympathized with the person in the picture.

Results: There were no significant differences between ASD and TD children on EE (t(34) = 1.18 , p = .247) or arousal (t(34) = .79 , p = .437). However, the groups differed on CE (t(34) = 2.09 , p = .044), with lower accuracy in the ASD group. Additionally, there were significant positive correlations between arousal and EE (ASD, r = .916, p < .001 TD, r = .801, p < .001). CE and arousal were also negatively correlated in the ASD group (r = -.619, p = .005).

Conclusions: Consistent with prior studies, children with ASD were less accurate at explicitly identifying emotions (CE) but demonstrated intact emotional empathy. Strong positive correlations between arousal and EE are consistent with the somatic marker hypothesis of emotion (Damasio et al.,1991). The ASD group's ability to correctly identify emotions (CE) decreased as arousal increased, suggesting a possible role of anxiety. The MET-J dissociated CE deficits from intact EE in this sample, confirming and extending previous findings in adults to children with ASD. Future directions include the use of physiological measures of arousal to validate the arousal ratings.
A growth based strategy for benchmark comparisons of a language intervention to a typical sample

Lauren H. Hampton, Megan Y. Roberts, Ann P. Kaiser

Keywords: Autism, Latent Growth Curve Modeling, Intervention, Language delays, Enhanced Milieu Teaching

Determining effectiveness of an intervention is often done utilizing pre-post comparisons. However, this fails to give us more sophisticated information such as a developmental trajectory (Curran & Muthen, 1999). Using latent growth curve models to benchmark progress in an intervention relative to a typical sample allows researchers to not only examine differences between groups in scores but also in rate of change. In the current study, language intervention results were examined as compared to a notreatment group as well as an age-matched typical sample. Enhanced Milieu Teaching (EMT) with parent training was the intervention used to increase language skills in toddlers with language delays. Four research questions were addressed: a) Is parent-implemented EMT effective for improving language, as measured by a language sample, in language delayed toddlers as compared to a control group receiving community services only? b) is the slope of the intervention group more similar to a typical control group following intervention than the slope of the community services group? c) Does the slope of the number of different words used in a language sample for the intervention group predict standardized language scores? d) Does diagnosis with expressive language delay only, receptive and expressive language delay, or autism moderate the relationship of the intervention over time?

One hundred and eighty toddlers were included in this study: 85 typically developing, and 95 children with language delays (50 control and 45 treatment). Forty-five of the language delayed toddlers were randomly assigned to receive the 3-month EMT with parent training intervention (Kaiser & Roberts, 2013). Children were assessed at six time points: once prior to intervention, once following each month of intervention, and at six and twelve months following intervention. The intervention included one onehour clinic based sessions and one one-hour home visit each week. Parents were taught the intervention through a teach-model-coach-review format.

A multiple-group latent growth curve was fit to the data after examining more parsimonious models (Bollen & Curran, 2006). A random intercept model was fit at the post-intervention time point to examine group differences following intervention. Random linear slopes were fit to the model as well as fixed quadratic slopes.

Results indicated a significant difference among the three groups at post intervention for intercepts, and non-significant differences among the groups in linear slopes at post intervention. Although the intervention group was significantly improved over the community services group, the rate of growth for the intervention group was not significantly different from the rate of growth for the intervention group (Intervention mean: 8.95, Control group mean: 5.06, Typical sample mean: 5.06). Although the intervention group did not catch up to the vocabulary use in the typical group, this model allows for estimating the rate of change that must be achieved in intervention in order to close the gap. Implications for future research, intervention length and intensity, and future intervention research analysis will be discussed.
Frontal cortical changes after neuroplasticity-based cognitive training in survivors of childhood brain cancer

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Keywords: cognitive training, intervention, functional imaging, pediatric cancer,

Cognitive consequences of childhood brain cancer are pervasive and remain after the cancer has remitted. Research has shown that survivors of brain tumors experience a significant and persistent decline in cognitive ability following treatment, and there is no evidence for a spontaneous recovery. Without intervention, these pervasive deficits are likely to adversely affect all areas of behavior. Thus, remediation of these deficits is of great importance to improving the quality of life of these individuals. However, relatively little is known about the efficacy of intensive and noninvasive cognitive training in this population. We used a neuroplasticity-based brain fitness program to train perception, attention and working memory in children who have undergone invasive treatments for brain tumor and documented changes in frontal cortical activity before and after training.

We have recruited 24 survivors of brain tumors into this ongoing study. Half were randomized to complete computerized cognitive training (treatment condition) for 5 weeks followed by 5 weeks of no training (control condition). The other half started with the control condition for 5 weeks, followed by the cognitive training (treatment) for 5 weeks. We assessed neurocognitive functioning at baseline, post-treatment and post-control condition and used near infrared spectroscopy (fNIRS), a noninvasive functional imaging method to assess frontal cortical activity during a working memory task. We administered a comprehensive battery of standardized, computerized tests at each time-point to detect training-related changes in executive functioning and working memory.

14 participants have already completed CogMed training with good compliance, and have completed fNIRS before and after training. After training, participants showed increased oxy-Hb in mostly left prefrontal areas during the N-back working memory task. Participants also performed faster on a forced choice reaction time task, faster and more accurately on an executive function task, and more accurately on a social cognition task.

We then examined two subgroups based on treatment type: those participants who received surgery only (N=7) and those who received surgery plus adjuvant care (chemotherapy or radiation (N=7). The surgery-only group performed more accurately on a task of visual memory, and also improved in parentratings of executive function behaviors after training compared with the surgery+adjuvant care group. But the surgery+adjuvant care group showed more robust increase in the frontal oxy-Hb levels after training than the surgery only group.

These results suggest that cognitive training may lead to normalization of task-related frontal cortical activity for some child brain cancer survivors, as well as improvements in a measure of executive function and social cognition. However, training-related functional and behavioral changes may depend somewhat on type of tumor treatment received.
Differences in How Monolingual and Bilingual Children Learn Second Labels for Familiar Objects

Lindsey W Rowe, Megan M Saylor

Keywords: Language Development, Monolingual/Bilingual

Monolingual children sometimes resist learning second labels for familiar objects (e.g., that a boat can also be called a skiff). This may be due to their tendency to adhere to mutual exclusivity, which is the principal that an object should have only one name. It is less clear whether or not bilingual children observe this constraint. A first study demonstrated that bilingual preschoolers were more likely to accept second labels for familiar objects and were more sensitive to information about the relationship between the familiar label and the new word (e.g., "a skiff is a kind of boat") than were monolingual preschoolers, who did not reliably learn the new words. In a second study, monolingual preschoolers were offered additional information about the relation between the familiar word and new word. This extra information helped them accept a second label for the objects. These studies suggest that, while both monolingual and bilingual preschoolers adhere to mutual exclusivity to some extent, bilingual preschoolers are better able to set aside this bias in order to learn an additional label for a familiar object.
Braille Reading Comprehension

Mackenzie E. Savaiano

Keywords: braille, vocabulary

Vocabulary is a key element of background knowledge. Decoding is integral to the reading process, but is only helpful for comprehension if the resulting word is part of the reader's vocabulary (NICHD, 2000). There is a transactional relationship between vocabulary, comprehension, and amount of reading (Nagy, 2005). Fewer experiences lead to less complete general background knowledge and vocabulary to draw upon during word identification. For students who read braille, the age of onset of blindness, visual diagnosis, amount of functional vision, and presence of additional disabilities are only a subset of factors that could potentially affect the quality and quantity of early learning experiences. As a result, students who read braille may have less exposure to text, which may affect vocabulary acquisition (Savaiano et al., 2013).

Rosenthal and Ehri (2008) taught unfamiliar words to groups of 2nd and 5th grade children by defining words, depicting words, and using words in sentences. One set of words had the spellings visible, and the other set did not. The spellings helped students remember the meanings of words compared to the words without spellings. Although this association has the potential to facilitate the efficiency of word learning, written words are not often included in vocabulary instruction (Ehri & Rosenthal, 2007).

This study examined whether the presence of a target word in braille facilitated vocabulary acquisition for three students who read braille. Two strategies were compared using an adapted alternating treatments single-subject design. The with word (WW) strategy had four components: (a) the target word was presented in braille on a flashcard, (b) the target word was spoken aloud, (c) the target word definition was spoken aloud, and (d) the target word was used aloud in a sentence. Auditory vocabulary instruction for students who read braille typically involves verbal instruction, in which words and their definitions are spoken aloud without being presented in braille (components b-d). Specifically, this study addressed the following research questions: Do students who are blind learn (1) the meanings of words more efficiently and (2) to spell words more accurately via WW vocabulary instruction or auditory vocabulary instruction?
Services for Children with ASD: Comparing Rural and Non-Rural Communities

Maria P. Mello, Samantha E. Goldman, Richard C. Urbano, Robert M. Hodapp

Keywords: Autism Spectrum Disorders, Services, Rural

Background: Although the diagnosis of autism spectrum disorder (ASD) involves atypical social interactions, communication deficits, and restricted or stereotyped behaviors, children with ASD also show other, co-occurring behavior problems. Unfortunately, little is known about how these co-occurring symptoms should inform targeted interventions for these children and how these interventions might vary by age. Compared to children with other disabilities, children with ASD often receive a high number of services with a lack of a standardized treatment approach. This study examines how service receipt changes over age and whether services are tied to the presence or severity of specific behavioral problems.

Methods: Respondents included 361 parents of children ages 2-21 with ASD who completed an online survey. Children had a mean age of 10.02 years (SD = 5.12) and received an average of 3.40 (SD = 2.13) services (range from 0 to 10 services). Parents reported a mean behavior problem severity score of 2.43 (with 1 = no problem and 4= severe problem) on 12 behavior items from the Parental Concerns Questionnaire (McGrew et al., 2007).

Results: Factor analysis with varimax rotation was first performed on these 12 behavior items and two factors were extracted. The first, named Psychiatric Behaviors, explained 27.19% of the variance and the second, named Autism Characteristics, explained an additional 22.78%. A 2x2 ANOVA was then performed for service provision by age group (2-9 and 10-21) for the Psychiatric Behaviors and Autism Characteristics factors. Results showed that those receiving Special Education, PT/OT, Health, and Respite had higher scores on the Autism Characteristics factor, regardless of age group. There was also a significant interaction (p<.05) between Speech and age group. For the Psychiatric Behaviors factor, there was a significant relationship with age for Special Education, Health, Counseling/Psych, and Respite services, with a significant interaction (p<.05) between service provision and age for Speech and Behavior Support services.

Conclusion: Results show a relationship between some commonly co-occurring behavior problems reported for children with ASD. These two factors, Psychiatric Behaviors and Autism Characteristics, may be useful in linking need to service and making decisions about important supports for children with ASD. Our results also support the idea that treatments vary by age group, across disability severity. Future research should confirm the reliability of parental reporting with professional reports of behavior problems and services.

Key References:
Long-Term Memory Deficits in Schizophrenia - Preserved and Compromised Cognitive Processes Implicating Differences in Prefrontal-Temporal Lobe Circuitry

Megan Ichinose, Joshua McCluey, Meghan Collins, Michael Geoghegan, Sean Polyn, & Sohee Park

Keywords: schizophrenia, working memory, long-term memory

Memory deficits have been acknowledged as a core subtype of cognitive impairments associated with schizophrenia (SZ). Long-term memory (LTM) impairment assessed via free recall has specifically emerged from meta-analyses with stable and large effect sizes. However, the exact nature of dysfunction within LTM processes is unknown, particularly in its relation to other core cognitive deficits involving working memory (WM) and its specific contribution to the SZ symptom profile. Thus the present study examined memory organization within the greater construct of long-term memory ability for patients with SZ in relation to their clinical symptoms and WM performance. Nineteen SZ outpatients and 16 matched healthy controls (HC) completed (1) a verbal free recall task tapping LTM and (2) a number/letter sequencing task tapping WM. The groups were matched for age, sex, race, handedness, and IQ. Overall LTM performance was assessed by immediate and delayed recall on the free recall task, while LTM organization was computationally operationalized as follows: word list position (serial position curve), contiguity of recalled items (temporal distance factor), semantic organization of recalled items (semantic distance factor), and the probability that certain words would be the first recalled (probability of first recall). Overall LTM (immediate and delayed) was impaired in SZ. Despite general reduction in recall, LTM organization appeared intact as indicated by similar serial position curves, temporal distance factors, semantic distance factors, and probability of first recalls compared to HC. As expected, WM performance was impaired in SZ compared to HC. For HC, WM performance correlated with overall LTM performance. This relationship was absent in SZ, and WM-LTM correlations were significantly different between groups. Such results implicate differential recruitment of WM circuitry for free recall in SZ compared to HC. Given well-replicated findings of impaired prefrontal cortex (PFC) function during WM in SZ and the pivotal role of medial temporal lobe (MTL) in LTM, results implicate the role of PFC in LTM and/or differences in PFC-MTL activity during LTM for SZ. In SZ, better performance for delayed LTM was associated with exacerbated delusion symptomology, pointing to an intriguing avenue of research examining formation and maintenance of delusions and LTM. Additionally, LTM performance was negatively correlated with avolition and apathy, implying a role for cognitive deficits in negative symptoms. These results offer a unique analysis of LTM ability in SZ, such that processes involved in memory organization might be intact despite clear impairments in WM and LTM performance. Contributions of WM to LTM in SZ should be further explored, with findings suggesting a disconnect between the two processes specific to SZ.
Multimodal evaluation of sensory processing and neurodevelopment in NICU infants

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Keywords: Neurodevelopment, ERPs, Multi-sensory

Background: Newborns, both term and pre-term, who require time in the Neonatal Intensive Care Unit (NICU) disproportionally account for 25-50% of children with significant motor, cognitive, visual and hearing impairments. However, evidence-based neuroprotective strategies or even good prognostic tools are lacking for these infants, which in turn presents a challenge to gathering meaningful data. While predictions for many traumatic event outcomes, such as massive intracranial hemorrhage, are fairly straightforward, sensory abnormalities are not usually identified until well into school age, when deficits begin to present themselves.

Objective: There is a pressing need to develop quantitative measures to predict and evaluate sensory function and longer-term neurodevelopment in children during or shortly after their NICU stay in order to provide timely and effective therapy and counsel families appropriately. Infancy is a period of maximal plasticity during which the brain can recover from massive insult. Therefore, we hypothesize that our approach using Event-Related Potentials (ERPs), which indexes the EEG time-locked to the presentation of sensory stimuli, would allow for characterization of brain responses to sensory stimuli, without engaging their attention to the stimulus or requiring active participation.

Methods: A high-density array of 128 electrodes embedded in soft sponges is used to record ERPS. Air puffs will be delivered using a custom made apparatus with two flexible nozzles: one placed on the palm of the infant (puff condition), and the other placed in proximity but directed away (sham condition). A monotone "Ga" sound stimulus is also presented in coordination with the other conditions. The recorded data is later filtered and screened for motor/ocular artifacts, and then followed by manual review. For a data set to be included in the statistical analyses, individual conditions would include ≥10 usable trials.

Results: For this total study, we examined 65 infants, 28 pre-term and 31 term infants with complete data, at full equivalent age. We demonstrated that cortical responses to air puffs display characteristic patterns of detection (P50), intrinsic attention modulation (N140) and more advanced processing (P200) as we have measured in older children (Fig. 2). These responses are significantly different than those elicited from a sham stimulus (same auditory experience but no air puff delivered to the hand).

Conclusions: Our ERP paradigm can detect somatosensory responses even in the absence of deliberate attention to the stimuli, and that these responses are even more differentiated in older infants, supporting feasibility in 12-24 month-old children.
Vocational trajectories for high-functioning adults with autism spectrum disorders

Natalie A Henninger, Marsha R Mailick, Julie L Taylor

Keywords: autism spectrum disorders, transition to adulthood

Introduction: Studies have consistently shown high rates of unemployment among adults with autism spectrum disorders (ASD). Although high-functioning adults with ASD have better vocational outcomes on average than those with comorbid intellectual disability (ID), Taylor and Seltzer (2011) found that adults with ASD without ID were three times more likely to have no vocational activities. The present study extends this work by examining trajectories and predictors of vocational activities for adults with ASD without ID over time.

Methods: Participants were 76 adults with ASD without ID who were part of a larger longitudinal study. About one-fifth (22.4%) of the sample was female, and the age range was 18 to 47 years (M=23.8 years). Data were collected at six time points over 10 years, and those who had at least three time points of post-high school vocational/educational data were included. Trajectory groups were determined using Vocational Index Scores collected at each time point, ranging from 1 (no activities) to 9 (competitive employment or postsecondary education; Taylor & Seltzer, 2012). Individual characteristics used to predict vocational trajectories included demographics, autism symptoms, behavior problems, activities of daily living, and various aspects of maternal mental health.

Results: One quarter of adults (n=19, 25.0%) were consistently in competitive employment and/or postsecondary education (PSE). A significant proportion of adults (n=25, 32.9%) was never engaged in competitive employment or PSE, instead spending time in supported employment, sheltered settings, volunteering, or doing nothing. Most commonly, trajectories consisted of a combination of competitive employment/PSE and less independent vocational activities (n=32, 42.1%).

Gender predicted consistency in competitive employment/PSE ($\chi^2=6.38, p<.05$). No women were consistently engaged in these activities, but were evenly split between being sometimes (n=6) or never (n=9) engaged in competitive employment/PSE. In contrast, males were fairly evenly distributed across the three groups (consistent, n=19; sometimes, n=19; never, n=23). Adults who had more autism symptoms were significantly less likely ($F=6.28, p<.01$) to have ever had competitive employment or PSE activities (M=14.05), compared with those who were sometimes (M=11.0) or consistently (M=9.41) engaged in either of these activities.

Conclusion: Many adults with ASD without comorbid ID struggle to achieve and maintain independence in vocational activities. These results suggest that it may be particularly difficult for women to achieve consistency in competitive employment or PSE; gender differences in vocational activities for adults with ASD should be further explored. Having more autism symptoms differentiated adults who never had competitive employment or PSE, suggesting that interventions targeting social communication and communication and repetitive behaviors may promote more independence in vocational activities for adults with ASD without ID.
Vanderbilt Kennedy Center Science Day 2014 Abstracts

Poster: 91 Session: 1  
Presenter: Peng Peng (kevpp2004@hotmail.com)  Lab PI: Douglas Fuchs

Drill and Practice Versus Rehearsal: An Experimental Study of Two Approaches to Strengthen Working Memory and Comprehension among Young Children

Peng Peng, Douglas Fuchs

Keywords: working memory, drill and Practice, rehearsal strategy, listening comprehension, young children

Researchers are increasingly interested in the effects of working memory (WM) training. However, it remains unclear whether it strengthens WM and comprehension among young children. In this study, we investigated whether training verbal WM would improve verbal WM and passage listening comprehension, and whether training effects differed between two approaches: drill and practice vs. rehearsal. Fifty-eight first-grade children were randomly assigned to three groups: WM drill and practice, WM rehearsal training, and controls. The two training groups received one 35-minute session of verbal WM training on each of 10 consecutive school days, totaling 5.8 hours. Both groups demonstrated significant growth on trained WM tasks, with the rehearsal group showing greater growth. Compared to controls, the rehearsal group also made significant improvement on, non-trained WM tasks, passage listening comprehension, and retell. The drill and practice group showed significant improvement on passage listening comprehension. The frequency of rehearsal strategy use in the drill and practice group was positively related to their comprehension improvement. Findings suggest that brief but intensive training on verbal WM is feasible with young children. The rehearsal strategy may link verbal WM training to comprehension improvement.
How does that make you feel? The role of emotional awareness on empathic deficits in autistic and schizotypal traits

Rachel V. Aaron, Taylor L. Benson, Sohee Park

Keywords: alexithymia, emotions, empathy,

Empathy is a broad and multifaceted construct, involving a complex combination of affective and cognitive processes. Most psychologists agree that empathy requires: an affective response to another person, cognitive capacity to adopt another’s perspective, and monitoring mechanisms that modulate inner states (Decety & Moriguchi, 2007). Given this, it is not surprising that alexithymia, difficulty identifying and describing one’s own feelings, is consistently correlated with empathy. The "shared network" model of empathy offers a possible explanation for this connection: this theory suggests the same neural networks involved in processing one’s own emotions are involved in representing the emotions of another; thus, an inability to represent one’s own emotions likely leads to empathic deficits. Recent work has expanded on this possibility, reporting that empathic brain responses in the insula are modulated by levels of alexithymia but not autism (Bird et al. 2010). The current study sought to expand these findings by considering how alexithymia relates to empathic deficits in those with autistic traits, and additionally, schizotypal traits, in a nonclinical sample. We administered the following questionnaires to a nonclinical sample: TAS-20 (to assess alexithymia), AQ (to assess autistic traits), SPQ (to assess schizotypal traits), and IRI (to assess empathy). Using bootstrap mediation technique, we found that alexithymia mediates the significant correlations between SPQ and IRI, and AQ and IRI. The results highlight the role of alexithymia in empathy in a nonclinical population, and further point to the importance of examining the effect of alexithymia on empathic deficits in autism and schizophrenia.
Comparison of the Clinical Profiles of 1Year Olds and 2Year Olds with Autism Spectrum Disorders

Rachel E. Aiello, Kristeena Jenkins, Zachary Warren, & Cassandra R. Newsom

Keywords: Autism Spectrum Disorders, Developmental Profile, Toddlers, Early Diagnosis, Assessment

Background: Accurate, stable diagnosis of ASD may be possible within community settings during the second year of life for some children (Corsello et al., 2012; Guthrie et al., 2012), and young children with ASD receiving early behavioral intervention demonstrate substantial gains in functioning (Dawson et al., 2010, 2012; Warren et al., 2011). Numerous screening initiatives (AAP, CDC Act Early) have pushed for identification prior to age two. However, CDC figures suggest a majority of individuals with ASD are not diagnosed until after age 3. To date, few studies outside of high-risk sibling protocols have characterized the developmental profiles of toddlers with ASD in the 1 and 2year age range. It remains unclear whether children identified before age two evidence more concerning clinical profiles (e.g., lower cognitive abilities, severe impairments of adaptive functioning, higher levels of ASD symptoms) than children identified at later ages. Understanding such differences has implications for programs targeting universal screening and very early diagnosis.

Objectives: This project explored the developmental profiles of toddlers diagnosed with ASD in the 2nd year of life in comparison to children diagnosed in the 3rd year of life in a well-characterized university clinical research database. We examined whether younger children evidenced profiles of more significant delays and impairments.

Methods: Participants included children seen through university-affiliated developmental clinics as well as children participating in a variety of research protocols (e.g., genetic collections, infant sibling studies, intervention protocols). 488 children below the age of 36 months (n = 63 <24 months; n = 425 between 24 and 35 months) were included in the sample. All children were newly diagnosed with ASD. Diagnostic measures included the MSEL, ADOS, and VABS. Child demographics including gender, rural/urban setting, and sibling status via caregiver report were also utilized.

Results: A series of preliminary independent samples t-tests were conducted to compare differences in developmental profiles for children below 24 months of age and children between 24-35 months of age. There was a statistically significant difference in overall performance of the MSEL composite for children with ASD diagnosed before 24 months of age (M = 61.4, SD = 13.1) compared to those diagnosed between 24-35 months of age (M =57.7, SD =14.8) scores, t(475) = 2.00, p <.05. No differences were obtained for the VABS Composite scores however, differences were observed within the VABS Socialization domain between the below 24 months group (M = 73.4, SD = 6.42) and the 24-35 months group (M = 68.8, SD = 8.43), t(471) = 2.31, p <.05. No differences were observed in ADOS Comparison scores between the two groups.

Conclusions: Preliminary results suggest that children identified before 24 months of age do not evidence patterns of more pronounced delay than children diagnosed after two. In fact, children identified before 2 demonstrated higher cognitive and adaptive behavior scores. This finding suggests that early identification efforts aimed at identifying very young children are not simply identifying children with more severe delays.
The Effects of Auditory and Visual Stimulation on Exploration in Infancy

Samantha J. Gustafson, Amy Needham, Anne Marie Tharpe

Keywords: Infant Development, Hearing Loss, Exploration, Auditory & Visual Stimulation,

Deafness in infancy can produce developmental delays in language, social, and behavioral development (Marschark, 1993). The majority of research on prelingual deafness explores the effect of auditory deprivation upon language and speech development. One area lacking thorough investigation is environmental exploration, which involves engagement with various objects that infants encounter through tactile manipulation and visual attention. Because infants use auditory information to learn about their surroundings, infants with hearing loss may show different exploratory patterns when compared to infants with normal hearing. Infants' attention to auditory and visual modality cues can provide important information about their perceptual experiences (Lansink et al., 2000). Thus, studying how infants with hearing loss and infants with normal hearing respond to auditory and visual stimulation might reveal the sensory focus of their attention and learning. During this study, an experimenter demonstrated how to activate a toy box that produced a visual or auditory stimulus when activated. The auditory and visual stimulus boxes were presented sequentially and then simultaneously. The preliminary results of this study show that during both sequential and simultaneous presentations, infants with hearing loss displayed longer looking times and length of stimulus activation for the visual stimulus than the auditory stimulus.
"What does that mean?" Exploring how children respond to unknown words

Rebecca M Jacobson, Megan M Saylor

Keywords: Language Development

Word recognition is an early stage process in language comprehension that supports recognition of familiar, known words. However, this early process may also support the ability to recognize when a word is new or unknown. This study investigates whether language experiences, age and vocabulary level affect children's ability to recognize that a word is new. Preschoolers were read books containing several mentions of an unknown word. Recognition was measured by whether children asked what the word meant. Thirty percent of children asked about the meaning of the novel word. Children who asked about the meanings of words had higher average vocabulary scores than children who did not ask about the new word. Age and language background (whether the child was bilingual or monolingual) were not significant predictors of asking behavior. These findings suggest that children who know more words are more likely to seek out information about new vocabulary. Future study could explore how to support this information-seeking behavior in children who know fewer words because they would benefit the most from information about new vocabulary.
Characterizing Language Impairment in High Functioning Autism

Rebecca L Johnston, Jennifer H Foss-Feig, Kimberly B Schauder, Mark T Wallace, Wendy L Stone, Sasha F Key, Zachary E Warren

Keywords: High Functioning Autism, Language

Background: Language impairments are a defining feature of autism spectrum disorders (ASD) (American Psychiatric Association, 2013). Previous research has found that children with autism were impaired across measures of language (Condouris, Meyer, & Tager-Flusberg, 2003), including expressive and pragmatic language. Language impairments in high functioning individuals with autism who have intact cognitive functioning are more subtle, with typical language skills and relative weaknesses in pragmatic use of language (Tyson et al., 2013). The objective of this study was to further characterize language functioning of high functioning adolescents children diagnosed with ASD.

Method: Twenty-seven children diagnosed with an ASD and 22 typically developing children, all between 10 to 13 years of age, participated in the study. Participants were matched for age, gender, and IQ, measured by the Wechsler Abbreviated Scales of Intelligence. The Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4) and Comprehensive Test of Phonological Processing (CTOPP) were used to evaluate several aspects of language functioning. First, independent samples t-tests were conducted to compare ASD and TD groups with regard to phonological awareness and memory, receptive and expressive language functioning, and language use in everyday contexts. Second, Pearson’s product moment correlations were performed within the ASD group to examine relations between aspects of language functioning and IQ and autism symptom severity, as measured by the ADOS Total Score.

Results: Results revealed that children with ASD had significantly lower scores with regard to phonological Memory as measured by the CTOPP Rapid Symbolic Naming Composite, and with verbal memory and receptive as measured by the CELF-4 Concepts & Following Directions, Recalling Sentences subtests and the Receptive Language Index. There were also significant differences present between the ASD and TD groups in the Speaking domain of the CELF-4 Observational Rating Scale, indicating a difference in use of language in everyday context, as rated by parents. Within the ASD group, significant relationships were present between phonological awareness and verbal IQ, performance IQ and verbal memory however, there was no significant relationship present between language vulnerabilities and severity of autism symptoms.

Conclusions: Results of this study suggest that even among high-functioning, verbal children with autism, there are subtle deficits in several aspects of language abilities and everyday use. Language weaknesses are associated with cognitive functioning in ASD, but less so with overall symptom severity. Thus, the relative contribution of language-related weaknesses to broader deficits in social communication remain to be further clarified.
Availability of BCBA Providers As a Barrier to Service Implementation in ASD

Rebekah P Travis, A. Pablo Juárez, Cassandra R Newsom, Zachary Warren

Keywords: Health Services, Policy and Rehabilitation

Background: According to the Centers for Disease Control and Prevention (CDC, 2012), an estimated 1 in 88 children and an estimated 1 out of 54 boys in the United States have an autism spectrum disorder (ASD). ASD is associated with enormous individual, familial, and societal costs across the lifespan (Amendah et al, 2011; Ganz, 2007). As such, effective early identification and treatment of ASD across resource-constrained environments is often considered a public health emergency (IACC, 2012). Early, intensive ASD behavioral intervention embedding the principles of ABA is supported by several systematic and metaanalytic reviews (Reichow et al., 2012, Warren et al., 2011). While clinicians who specialize in the diagnosis and treatment of autism spectrum disorders often recommend behavioral services, there are numerous barriers to access of such services across diverse populations and geographies. While many parents report being able to implement educational and/or early intervention services (e.g., IEP development, speech therapy, occupational therapy), in some communities only a minority of families are able to implement recommendations regarding ABA-based intensive services (Warren et al., 2013).

Objectives: The current study examined availability of providers as a potential barrier to services. Methods: Specifically, we examined the number of board-certified behavioral analysts across diverse geographies within the state of Tennessee in comparison to estimated numbers of children identified with ASD. This was done by county, region, and on a state level and tied to examinations of geography (e.g., rural/urban) and markers of income (SES). Results: There are currently only 260 Board Certified Behavior Analysts (BCBA) registered in the state of Tennessee (Behavior Analyst Certification Board, 2013), which has a 2012 population estimate of 6,453,243 (US Census Bureau, 2013). Given an estimated annual life birth rate of approximately 88,000, some 1,000 children with ASD are born in TN on an annual basis. On a state level this translates into 260 BCBA potentially available to serve 18,000 individuals under 18 with ASD and some 5000 individuals between 12-72 months of age. Several counties and zip codes did not have access to any BCBA providers with urban and insurance catchments having more access to providers. Conclusions: Given the available number of BCBAs within our state, specific recommendations for early intensive services delivered or even supervised by BCBAs may not be realistic. This finding has both potent ethical and service system implications for clinical providers.
The Relationship between Age, Severity, and Services for Children with ASD

Samantha E. Goldman, Maria P. Mello, Richard C. Urbano, & Robert M. Hodapp

Keywords: Autism Spectrum Disorder, Services, Behavior Problems

Background: Although the diagnosis of autism spectrum disorder (ASD) involves atypical social interactions, communication deficits, and restricted or stereotyped behaviors, children with ASD also show other, co-occurring behavior problems. Unfortunately, little is known about how these co-occurring symptoms should inform targeted interventions for these children and how these interventions might vary by age. Compared to children with other disabilities, children with ASD often receive a high number of services with a lack of a standardized treatment approach. This study examines how service receipt changes over age and whether services are tied to the presence or severity of specific behavioral problems.

Methods: Respondents included 361 parents of children ages 2-21 with ASD who completed an online survey. Children had a mean age of 10.02 years (SD = 5.12) and received an average of 3.40 (SD = 2.13) services (range from 0 to 10 services). Parents reported a mean behavior problem severity score of 2.43 (with 1 = no problem and 4= severe problem) on 12 behavior items from the Parental Concerns Questionnaire (McGrew et al., 2007).

Results: Factor analysis with varimax rotation was first performed on these 12 behavior items and two factors were extracted. The first, named Psychiatric Behaviors, explained 27.19% of the variance and the second, named Autism Characteristics, explained an additional 22.78%. A 2x2 ANOVA was then performed for service provision by age group (2-9 and 10-21) for the Psychiatric Behaviors and Autism Characteristics factors. Results showed that those receiving Special Education, PT/OT, Health, and Respite had higher scores on the Autism Characteristics factor, regardless of age group. There was also a significant interaction (p<.05) between Speech and age group. For the Psychiatric Behaviors factor, there was a significant relationship with age for Special Education, Health, Counseling/Psych, and Respite services, with a significant interaction (p<.05) between service provision and age for Speech and Behavior Support services.

Conclusion: Results show a relationship between some commonly co-occurring behavior problems reported for children with ASD. These two factors, Psychiatric Behaviors and Autism Characteristics, may be useful in linking need to service and making decisions about important supports for children with ASD. Our results also support the idea that treatments vary by age group, across disability severity. Future research should confirm the reliability of parental reporting with professional reports of behavior problems and services.

Key References:
Past Tense Marking in Oral Reading: A Clinical Marker for SLI in School-Age Children?

Krystal L. Werfel, Sarah E. Lorch, C. Melanie Schuele

Keywords: Specific Language Impairment, Tense-marking, School-age

This study evaluated the potential of past tense marking in an oral reading task to serve as a clinical marker of SLI in school-age children. The performance of elementary school children with SLI and children with typical language on past tense marking in an oral reading task was compared. Clinical implications are discussed.
Sticky Mittens Reaching Intervention Affects Infants' Looking

Sarah E. Wiesen, Amy Needham, Jane Hirtle

Keywords: infant, sticky mittens, size preference, reaching, object exploration

Previous studies show that as infants gain experience reaching and grasping, they overcome the appeal of visually salient, larger objects and begin to prefer smaller objects that are more graspable (Libertus, Gibson, Hidayatallah, Hirtle, Adcock & Needham, 2013, Newman, Atkinson, & Braddick, 2001). The present study builds upon these findings by asking whether providing early reaching experiences to 3-month-old infants would influence their object preferences. Specifically, could infants' preference for object size be influenced by brief simulated reaching experience?

Infants (n=32) were randomly assigned to passive training (n=17) or active training (n=15). Infants in the active group wore mittens with Velcro loop covering the palms. Wearing these mittens enabled infants to pick up and move lightweight toys with the edges covered in Velcro hook, even though these infants were not yet reaching independently. Infants in the passive group wore non-sticky mittens, and an experimenter manipulated small toys to provide a comparable visual experience. All infants participated in 8 minutes of mittens training; the mittens were put on immediately before and removed immediately after training. Two striped, cylindrical objects were presented to infants before and after training: one large cylinder (diameter = 18 cm) and one small cylinder (diameter = 5 cm). The experimenter presented the objects for 10 seconds outside of infants' reach and then for 20 s within infants' reach.

Previous research indicates that infants rapidly update their locomotion decisions to reflect their current bodily attributes. New walkers who donned heavy, lead-filled vests were more hesitant to walk down slopes, while toddlers who wore feather-filled vests did not adjust their walking (Adolph & Avolio, 2000). In accordance with these findings, we found that infants' visual preferences quickly responded to newly introduced reaching and grasping abilities when objects were presented within reach. A MANOVA, with phase (pre/post) as a within-subject factor and group (active/passive) as a between subject factor, was used to analyze infants' looking toward the objects. Infants who were able to interact with toys during training looked more toward the smaller, graspable object from pre- to post-training in comparison to infants who participated in the passive mittens training experience ($F(1,30)=4.22$, $p=.049$). Infants in the active group also looked less toward the large object from pre- to post-training compared to their peers in the passive group, $F(1,30)=2.11$, $p=.044$. On the other hand, infants' looking behaviors did not differ from pre- to post-training when the objects were outside of their reach. Thus, eight minutes of active sticky mittens training appears to sensitize infants to the graspsability of objects within reach.
Simple View of Reading in Young Adults

Sheryl L. Rimrodt, Hannah G. Rowland

Keywords: reading disorders

Reading disorders affect about 5-10% of the population and often persist into adulthood. The Simple View of reading comprehension highlights the transition from a beginning reader’s reliance on unfamiliar text-based skills (i.e., word identification) to the demands on older readers to integrate this text-based skill with language comprehension to construct meaning (i.e., Construction-Integration model). This study builds on the Simple View to examine the impact of factors beyond basic oral language skills on reading comprehension in young adults. Sixty-one 18-25 year old participants completed measures of reading comprehension, word identification, oral language, general cognitive ability, visual and verbal executive function, and self-report of ADHD. The first level of a hierarchical regression analysis supported the Simple View; namely, word identification and oral language each added significant unique variance to the model and together explained a significant proportion (27%) of the variance in reading comprehension. However, the unique variance of these predictors was encompassed and overall variance explained nearly doubled (51%) by the addition of the general cognitive measure but only in the verbal domain. Self-reported ADHD individually improved the model to explain 57% of the variance in reading comprehension subsuming the variance attributed to measures of executive function. Thus, the Simple View’s developmental approach to reading comprehension is relevant in young adult readers with additional variance captured both by verbal abilities and measures of attentiveness/impulsivity. Overall, the data suggests a literacy approach incorporating both basic word-level skills, as well as higher-order language-based cognitive function.
Effects of a Group Cognitive-Behavioral Depression Prevention Program on Psychosocial Functioning in At-Risk Adolescents

Steven M. Brunwasser, Judy Garber, V. Robin Weersing, Steven D. Hollon, David A. Brent, Gregory N. Clarke, William R. Beardslee, Frances L. Lynch, Tracy R.G. Gladstone

Keywords: prevention, depression, adolescence, psychosocial functioning, cognitive-behavioral intervention

Objective: To evaluate the effect of a cognitive behavioral (CB) depression prevention program on psychosocial functioning among adolescents at risk for depression (N = 316).

Method: Participants (ages 13-17) were eligible if they had (1) a parent with current or past depressive disorders, and (2) a past depressive episode, currently elevated but subdiagnostic baseline symptoms, or both. Adolescents were randomized to either a group CB prevention (CBP) program or usual care (UC). Psychosocial functioning was measured at five points: baseline, and at 3, 9, 21, and 33 months post randomization, using clinician ratings (Children’s Global Assessment Scale) and adolescent report (Social Adjustment Scale-Self Report). Independent evaluators, blinded to condition assignment, assessed for depressive episodes using the Schedule for Affective Disorders and Schizophrenia for School-Age Children -- Epidemiological Version (K-SADS-PL) and the Longitudinal Interval Follow-up Evaluation (LIFE). Latent growth curve (LGC) models were conducted to evaluate intervention effects on the rates of change (i.e., slopes) of the functioning measures. Parallel-process LGC models were used to test the hypothesis that intervention effects on functioning at follow-up were mediated by a reduction in risk for depressive episodes during the intervention phase. Confidence intervals for the indirect effects were calculated using 50000 Monte Carlo simulations.

Results: Youth in CBP showed significantly greater improvements in clinician-rated global functioning ($b = 0.172, 95\% \text{ CI } [0.025, 0.319])$ and self-reported family functioning ($b = -0.105, 95\% \text{ CI } [-0.203, -0.007])$ relative to UC, but not on self-reported primary role functioning or peer relationships. There were moderated-mediation effects whereby group differences in both global and family functioning at follow up were mediated by a reduction in risk for a depressive episode during the acute intervention phase among adolescents whose parents were not in an active depressive episode at baseline.

Conclusion: Findings indicate that targeted prevention may lead to enduring benefits in functioning. Future research should evaluate whether (1) CBP has effects on objective functioning measures, (2) effects endure into young adulthood, (3) symptom reduction precedes or follows gains in functioning, and (4) improvement in functioning offsets costs associated with program implementation.
Synesthesia & sense of self across the schizophrenia-spectrum.
Taylor L. Benson, Sohee Park
Keywords: Schizophrenia, Synesthesia, Dissociative Experiences, Multisensory Processing, Psychosis

BACKGROUND: Synesthesia is a neurological abnormality in which stimulation of one sense involuntarily yields a simultaneous perception in a separate sensory system. Patients with schizophrenia (SZ) have been hypothesized to have higher incidence of synesthesia compared to the general population. Supporting evidence for a link between synesthesia and SZ-spectrum disorders comes from preliminary research indicating that individuals with synesthesia (i.e., synesthetes) report greater levels of schizotypal personality compared to controls without synesthesia. However, to our knowledge, this hypothesized link between SZ and synesthesia has not yet been explicitly tested empirically in clinical populations. We hypothesize that synesthesia may confer risk for psychosis-proneness by increasing risk of dissociative self-disturbances. Indeed, anomalous or weakened sense of self was central to early theories of SZ and recent empirical studies have also documented disturbances in body ownership and increased susceptibility for dissociative experiences such as the out of body experience (OBE) in SZ. Dissociative experiences and OBEs have been investigated in non-clinical populations, but the link between psychosis proneness and these dissociative experiences is understudied. Furthermore, synesthetes have been hypothesized to be at greater risk for dissociative self-disturbances compared to individuals without synesthesia, but this question has not yet been addressed systematically. The current set of studies aimed to test our hypotheses that synesthesia predisposes individuals to psychosis-proneness via increased propensity for dissociative experiences.

METHODS: In Study 1, we investigated the prevalence of dissociative experiences in SZ patients and matched healthy controls (HC) using an OBE questionnaire and the dissociative experiences scale (DES). In Study 2, we investigated these same variables in a group of undergraduate students who had low or elevated risk for SZ. Students were assigned to elevated risk group if they endorsed more than 5 items on the Prodromal Questionnaire (PQ-B). In Study 3, we investigated prevalence of dissociative experiences in relation to self-reported synesthesia in HC and a sample of SZ patients. All HC also completed the Schizotypal Personality Questionnaire (SPQ).

RESULTS: SZ patients reported greater levels of synesthesia compared to HC. Synesthetes reported greater levels of positive schizotypal traits than individuals without synesthesia. Furthermore, synesthetes were more likely to report OBE history & more dissociative experiences than individuals without synesthesia. Similarly, individuals with OBE history report greater levels of synesthetic absorption than those without OBE history. Finally, as hypothesized, levels of dissociative experiences were found to mediate the relationship between synesthesia and schizotypal personality in HC.

DISCUSSION: The current study is the first demonstrate a link between synesthesia & psychosis-proneness among clinical and healthy populations. Specifically, SZ patients reported greater levels of synesthesia compared to HC, and synesthetes reported greater levels of psychosis-proneness & schizotypal personality compared to individuals without synesthesia. Weakened sense of self may be central to the prodromal stage of SZ and dissociative experiences may be a latent risk factor for psychosis. Self-disturbances were more commonly reported among synesthetes compared to the general population. Likewise, individuals with OBE history reported greater levels of synesthetic absorption. Future research should utilize this fascinating sample of individuals (i.e., synesthetes) to learn more about how multisensory mechanisms contribute to sense of self and how these processes can become disturbed in individuals at risk for psychosis.
Family Quality of Life (FQOL) for Transition-Age Youth: Associated Factors

Thomas L. Boehm, Erik W. Carter

Keywords: Family Quality of Life, Educational Post-Secondary Transition Outcomes, Spirituality

Despite more than two decades of federally mandated transition services, far too many young people with developmental disabilities and their families are not thriving. Yet, relatively little is known about factors accounting for why some youth and their families report having a high quality of life and overall well-being, while others do not. This large-scale, mixed methods study focused on identifying exactly what helps young people and their families to flourish during this transition to adulthood. Phase 1 of the project involved a statewide study of 450 parents of children ages 13-21 with intellectual disability or autism. Parents completed a series of assessment measures, including the Beach Center Family Quality of Life Scale (Beach Center on Disability, 2006) and the Santa Clara Strength of Religious Faith Questionnaire - Short Form (SCSRF; Plante, Vallaey, Sherman, & Wallston, 2002). The FQOL scale assesses parents' level of satisfaction with different aspects of family life that may contribute to overall quality of life for the family. The final scale includes 25 items in the following five domains: Family Interaction (6 items), Parenting (6 items), Emotional Well-being (4 items), Physical/Material Well-being (5 items), and Disability-Related Supports (4 items). The SCSRF is a 5-item scale that measures a respondent's level of agreement with five statements related to religious faith (e.g., I pray daily, I consider myself active in my faith or congregation).

Phase 2 of the project involved individual interviews with 48 parents and their youth/young adult child with disabilities. Participants were drawn from Phase 1 of the project. Interviews typically lasted between 1-2 hours and explored key factors enabling these young people to live a "good life." Of particular interest were the strengths these young people exhibited and the contributions of spirituality to overall well-being.

Across both phases of the study, we are exploring the following research questions: How do parents of young people with disabilities describe their family's quality of life and child's well-being? What family-, child-, and community-level factors are associated with family quality of life and well-being? Descriptive and predictive analyses are being used to explore quantitative data gathered as part of Phase 1. Constant comparative analyses are being used to code qualitative data gathered as part of the Phase 2. Despite a large and growing literature addressing the areas of transition and quality of life, far fewer studies have explored the intersection of these two issues. Findings from this project have direct implications for practitioners charged with supporting youth with disabilities and their families during the transition to adulthood.
Children with hearing loss have known deficits in language and literacy skills. It is often thought that improving hearing will directly lead to gains in language and literacy. As part of a pilot project by Dr. Rene Gifford and Dr. Stephen Camarata (Vanderbilt University), seven children with cochlear implants had their cochlear implants optimized via spectral analysis to improve their speech perception. Children were tested on standard measures of speech and language before and after spectral analysis using the Goldman-Fristoe Test of Articulation (GFTA), Test of Auditory Comprehension of Language (TACL), and Woodcock Johnson - Following Directions Subtask (WJ-FD). Children scored below average on preanalysis assessments with means respectively of 75, 82, and 84, p<.05 while nonverbal intelligence measured on the Leiter-3 was within the broad range of typical (85-115) but actually above the population mean (m=110; p<.05). Six to twelve weeks after spectral analysis, children were again tested using the same standard measures. Although children's speech perception had improved (Gifford et al.), performance on standard measures did not improved (p>.10 on all measures). Improvement in speech perception was not associated with immediate improvements on standard measures of speech or language. These results suggest that future studies of speech and language intervention in children with CI are warranted.
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