Risky Decision Making in Neurofibromatosis Type 1: An Exploratory Study

Rachel K. Jonas, EunJi Roh, Caroline A. Montojo, Laura A. Pacheco, Tena Rosser, Alcino J. Silva, and Carrie E. Bearden

ABSTRACT

BACKGROUND: Neurofibromatosis type 1 (NF1) is a monogenic disorder affecting cognitive function. About one third of children with NF1 have attentional disorders, and the cognitive phenotype is characterized by impairment in prefrontally mediated functions. Mouse models of NF1 show irregularities in gamma-aminobutyric acid release and striatal dopamine metabolism. We hypothesized that youths with NF1 would show abnormal behavior and neural activity on a task of risk taking reliant on prefrontal-striatal circuits.

METHODS: Youths with NF1 (n = 29) and demographically comparable healthy control subjects (n = 22), aged 8 to 19 years, were administered a developmentally sensitive gambling task in which they chose between low-risk gambles with a high probability of obtaining a small reward and high-risk gambles with a low probability of obtaining a large reward. We used functional magnetic resonance imaging to investigate neural activity associated with risky decision making as well as age-associated changes in these behavioral and neural processes.

RESULTS: Behaviorally, youths with NF1 tended to make fewer risky decisions than control subjects. Neuroimaging analyses revealed significantly reduced neural activity across multiple brain regions involved in higher-order semantic processing and motivation (i.e., anterior cingulate, paracingulate, supramarginal, and angular gyri) in patients with NF1 relative to control subjects during the task. We also observed atypical age-associated changes in neural activity in patients with NF1 such that during risk taking neural activity tended to decrease with age in control subjects, whereas it tended to increase with age in patients with NF1.

CONCLUSIONS: Findings suggest that developmental trajectories of neural activity during risky decision making may be disrupted in youths with NF1.

Keywords: Decision making, Development, Functional MRI, Neurofibromatosis type 1, Phenotype–Genotype, Psychiatric disorders

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Neurofibromatosis type 1 (NF1; MIM 162200), a monogenic disorder caused by mutations in the neurofibromin gene on chromosome 17, is one of the most common single gene disorders affecting cognitive function (prevalence 1:3500) (1). Physical features include the formation of peripheral nerve sheath tumors, café-au-lait spots, and Lisch nodules (2). About one third of children with NF1 meet diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD), and the cognitive phenotype includes impairment in prefrontally mediated functions that encompass attention, working memory, and inhibitory control (3).

The NF1 gene codes for the neurofibromin protein, which acts as a tumor suppressor that modulates the Ras signaling transduction pathway (4). Neurofibromin, a large cytoplasmic protein, is a negative regulator of Ras and acts to keep it in its inactive, guanosine diphosphate-bound state. Mutations in the NF1 gene lead to compromised neurofibromin activity and thus overactivity of Ras, resulting in dysregulation of cell growth and proliferation.

Mouse models of NF1 have uncovered Ras signaling-dependent increases in gamma-aminobutyric acid (GABA) release (5–7) and deficits in plasticity that contribute to their learning and memory deficits. These mouse models have also shed light on irregularities in dopaminergic metabolism in this disorder (8). In NF1, tyrosine hydroxylase, a precursor to dopamine, is reduced, leading to lower dopaminergic signaling (3). In addition to increases in GABA release in the striatum (7), Brown et al. (9) found reduced levels of dopamine in this structure in Nf1 mutant mice and reduced rearing in response to novel objects, suggesting a dampened response to novel stimuli. In addition to treatments that target Ras signaling (9,10), drugs that increased dopaminergic levels (i.e., methylphenidate, L-DOPA) rescued these behavioral deficits (9). Another study in a mouse model of NF1 found that deficiencies in dopaminergic signaling also appear to contribute to deficits in learning and memory (11). In humans, the stimulant methylphenidate has been used to treat attentional deficits in patients with NF1, which acts by blocking dopamine reuptake.
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thereby increasing extracellular dopamine (12,13). Although it is still unknown how neurofibromin regulates dopamine homeostasis in the brain, a recent review of cognitive dysfunction in NF1 points toward dopamine as a possible molecular target for remediating cognitive and psychiatric symptoms in patients with NF1 (3). Recent evidence from animal models suggests that dopaminergic neurotransmission in the striatum plays a direct role in risky decision making in that the amount of cue-evoked dopamine release in the striatum of rats predicted individual differences in risky versus safe choices during task performance (14,15). Furthermore, individual differences in dopaminergic neurotransmission have been thought to underlie variability in risky decision making in humans (16). Lastly, although little work has been done on inhibitory control in patients with NF1, a recent study found impaired impulse control in children and adolescents with NF1 on a visual go/no-go task, which was associated with reduced electroencephalography correlates of inhibitory control (17). These authors also found reduced relative GABA levels in medial frontal regions of the brain in patients with NF1, as measured by magnetic resonance spectroscopy, that were directly related to severity of impulse control problems. This work warrants further investigation of decision-making processes in NF1 and their underlying neural substrates.

Based on these findings, we hypothesized that patients with NF1 would show abnormal behavior on a task of risk taking shown to be reliant on the striatum and orbitofrontal cortex. The Cake Gambling Task (18) was developed as a child-friendly task to measure risky decision making with varying amounts of potential reward. Participants are asked to choose between low-risk gambles with a high probability of receiving a small reward and high-risk gambles with a low probability of obtaining a large reward. To date, this task has been used to investigate risky decision making in typical development; findings indicate that healthy youths tend to make riskier decisions as the potential reward is increased, and that risk taking in the low-reward conditions tends to decrease with age (18). Functional magnetic resonance imaging (fMRI) results revealed that risky decisions were associated with increased activation in the ventromedial prefrontal cortex (PFC) and ventral striatum (VS), whereas cautious choices were associated with activation in the dorsolateral PFC. Interestingly, this study also observed an adolescent-specific peak in ventromedial PFC activation while making risky decisions and an adolescent-specific peak in the VS when receiving reward feedback. The authors also found that older participants showed decreased activation in the dorsal anterior cingulate cortex during risky decision making. Furthermore, the tendency to make risky decisions was associated with decreased activation in the anterior cingulate cortex and lateral orbitofrontal cortex (19,20).

To our knowledge, no studies of reward-based decision making have been conducted in youths with NF1. Given the neurophysiological results in mouse models and the behavioral profile of NF1, we predicted that youths with NF1 would be more risk averse than healthy individuals, particularly when the potential reward is high. Because of the increases in GABA-mediated inhibition previously documented in the PFC of NF1 mouse models and associated hypopresentation of specific prefrontal structures in NF1 subjects (7), we hypothesized that patients with NF1 would not show the expected increases in neural activity in ventromedial PFC during risky decision making or increases in dorsolateral PFC activity during safe decision making. Consequently, we also anticipated altered age-related trajectories during both risky and safe decision making in patients with NF1. In addition, we predicted that the relationship between individual risky decision making and neural activity may differ in patients with NF1 versus control subjects. Lastly, based on findings in the mouse model indicating reduced dopamine levels and abnormal reward sensitivity (8), we predicted that patients with NF1 would not show an increase in VS activity when receiving positive feedback.

METHODS AND MATERIALS

Participants

In total, 51 participants (29 patients with NF1 and 22 healthy control subjects), aged 8 to 19 years, were included in the study. Participants in the study were recruited from three primary sources: 1) the Children’s Hospital Los Angeles Neurofibromatosis Clinic, a major NF1 referral center for the greater Los Angeles region; 2) local Children’s Tumor Foundation and Neurofibromatosis Network family educational symposia; and 3) NF-related websites as well as http://www.clinicaltrials.gov. All aspects of the research study were granted institutional review board approval by the University

Table 1. Demographic Characteristics of Study Participants

<table>
<thead>
<tr>
<th></th>
<th>NF1 (n = 29)</th>
<th>Control Subjects (n = 22)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean (SD) [Range]</td>
<td>11.93 (2.64), [8–16]</td>
<td>12.73 (3.49), [8–19]</td>
<td>.381</td>
</tr>
<tr>
<td>Gender</td>
<td>14 M, 15 F</td>
<td>13 M, 9 F</td>
<td>.443</td>
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<tr>
<td>Ethnicity, % Latino</td>
<td>38</td>
<td>32</td>
<td>.651</td>
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<tr>
<td>Full Scale IQ, Mean (SD)</td>
<td>93.79 (2.95)</td>
<td>112.50 (3.33)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>ADHD Diagnosis, %</td>
<td>41</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Participant Education, Years</td>
<td>6.55</td>
<td>6.95</td>
<td>.637</td>
</tr>
<tr>
<td>Highest Parental Education, Years</td>
<td>15.65</td>
<td>16.59</td>
<td>.278</td>
</tr>
</tbody>
</table>

Usable functional magnetic resonance imaging data were available on 36 participants (NF1: n = 18; control subjects: n = 18). Seven of the NF1 patients with ADHD were taking psychostimulant medication at the time of testing. ADHD, attention-deficit/hyperactivity disorder; F, female; M, male; NF1, neurofibromatosis type 1.

*p < .001.
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