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The impacts of pesticide and nicotine exposures on functional brain networks in Latino immigrant workers

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ABSTRACT

Latino immigrants that work on farms experience chronic exposures to potential neurotoxicants, such as pesticides, as part of their work. For tobacco farmworkers there is the additional risk of exposure to moderate to high doses of nicotine. Pesticide and nicotine exposures have been associated with neurological changes in the brain. Long-term exposure to cholinesterase-inhibiting pesticides, such as organophosphates and carbamates, and nicotine place this vulnerable population at risk for developing neurological dysfunction. In this study we examined whole-brain connectivity patterns and brain network properties of Latino immigrant workers. Comparisons were made between farmworkers and non-farmworkers using resting-state functional magnetic resonance imaging data and a mixed-effects modeling framework. We also evaluated how measures of pesticide and nicotine exposures contributed to the findings. Our results indicate that despite having the same functional connectivity density and strength, brain networks in farmworkers had more clustered and modular structures when compared to non-farmworkers. Our findings suggest increased functional specificity and decreased functional integration in farmworkers when compared to non-farmworkers. Cholinesterase activity was associated with population differences in community structure and the strength of brain network functional connections. Urinary cotinine, a marker of nicotine exposure, was associated with the differences in network community structure. Brain network differences between farmworkers and non-farmworkers, as well as pesticide and nicotine exposure effects on brain functional connections in this study, may illuminate underlying mechanisms that cause neurological implications in later life.

1. Introduction

Latino immigrant workers employed on farms experience chronic exposures to cholinesterase-inhibiting pesticides such as organophosphates and carbamates (Arcury et al., 2010; McCauley et al., 2013). Such exposure to pesticides could place this vulnerable population at greater risk for the development of neurological dysfunction (Casida and Durkin, 2013; Hernandez et al., 2016; Kim et al., 2017). A recent longitudinal study by Quandt et al. (Quandt et al., 2015) showed that total cholinesterase, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activities in farmworkers are decreased during the agricultural season compared to non-farmworkers. Although the role of long-term exposures to low to moderate levels of pesticides remains controversial (Nees, 2015), a growing body of studies indicates that chronic exposure to cholinesterase-inhibiting pesticides is significantly related to cognitive impairment (Munoz-Quezada et al., 2016; Jayasinghe, 2012). The long-term effects of exposures to pesticides may include an increased risk of developing depression

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(Beseler et al., 2008) or neurodegenerative disorders such as Alzheimer's disease (Parron et al., 2011) and Parkinson's disease (Mostafalou and Abdollahi, 2013; Moisan et al., 2015; Brouwer et al., 2015).

Tobacco farmworkers are not only exposed to pesticides, but also experience nicotine exposure through dermal absorption. Tobacco farmworkers can have systemic nicotine levels that are comparable to regular smokers (Arcury et al., 2016; Quandt et al., 2001). While it is known that large doses of nicotine are toxic (Lavoie and Harris, 1991; Mayer, 2014), many studies have indicated that lower, nontoxic doses of nicotine improve cognitive performance through modulating the release of several neurotransmitters including acetylcholine and dopamine (Heishman et al., 2010; Froeliger et al., 2009). An interesting finding is that nicotine may actually be protective against the development of Parkinson's disease (Barreto et al., 2015; Kiyohara and Kusuhara, 2011). Co-exposure to pesticides and nicotine is particularly interesting since both cholinesterase-inhibiting pesticides and nicotine alter cholinergic neurotransmission. Pesticides increase cholinergic neurotransmission by blocking the degradation of the acetylcholine. Nicotine, on the other hand, increases cholinergic neurotransmission by directly binding to the acetylcholine receptor.

The basal forebrain cholinergic system has projections that broadly innervate the cerebral cortex and subcortical nuclei. Changes in cholinergic neurotransmission could therefore have far-reaching rather than local, brain effects. Thus, studies aimed at evaluating the neurobiological changes associated with exposure to pesticides and nicotine would benefit by techniques that examine the brain as an integrated system rather than a collection of isolated brain areas.

Functional brain network analyses that use resting-state functional magnetic resonance imaging (rs-fMRI) have demonstrated great promise in examining systemic brain changes across health and disease (Sporns and Betzel, 2016; Bullmore and Sporns, 2009; Bassett and Bullmore, 2009). FMRI, as a non-invasive technique, is sensitive to changes in blood oxygenation that occur in response to changes in brain acidity. The blood-oxygenation level-dependent (BOLD) signal is sensitive to the changes in the relative amounts of blood oxyhemoglobin (higher) and deoxyhemoglobin (lower) that occur with increased neural activity (Ogawa et al., 1990a). A typical fMRI study is performed by collecting multiple (often hundreds) scans of the brain to identify the BOLD signal fluctuation that occur over time. Rs-fMRI measures the spontaneous fluctuations of the BOLD signal when the participant is not performing an explicit task (Ogawa et al., 1990b; Dosenbach et al., 2010). Approximately 95 percent of the brain metabolism occurs due to these spontaneous fluctuations (Raichle and Mintun, 2006).

The statistical association or dependency among BOLD signals from different parts of the brain image is referred to as functional connectivity (Ogawa et al., 1990b), and represents the functional interactions among different brain areas. Brain network analyses are based on graph theory and evaluate the connectivity patterns across the entire brain rather than focusing on connectivity to and from a single brain area (Simpson and Laurienti, 2016). Brain networks and graph theory methods are growingly used in studies of the human brain because these methods examine the brain as an integrated system (Sporns, 2013). Within a systems view of the brain, circuits are critical for normal and abnormal neurological processes rather than individual brain areas. Brain network analyses are proving to be clinically meaningful in studies of neurodegenerative disorders such as Alzheimer's (Rombouts et al., 2005; Wang et al., 2006, 2007; Vemuri et al., 2012) and Parkinson's (Szewczyk-Krolikowski et al., 2014; Tessitore et al., 2012) diseases, as well as for evaluating brain changes associated with smoking (Janes et al., 2012; Vergara et al., 2016).

This study used brain network analysis of rs-fMRI data and a mixed-effects modeling framework (Simpson and Laurienti, 2015) to compare brain network connectivity patterns between Latino immigrant workers engaged in farm work to those not engaged in farm work. The network analysis was used to characterize global as well as local brain connectivity patterns. This study provides important evidence for the potential neurobiological impacts of pesticide and nicotine exposures on the brains of Latino farmworkers.

Table 1
Study Population Characteristics.

Participant Characteristics	Farmworkers (n = 48)	Non-Farmworkers (n = 26)	*p-value
Age	40.33 ± 6.99 (Min/Max: 31/71)	43.61 ± 10.49 (Min/Max: 30/58)	**0.1108**
Education			**0.0654**
0-6 grade (Edu1)	17 (35.4%)	7 (26.9%)	
7–11 grade (Edu2)	24 (50.0%)	9 (34.6%)	
12 grade or more (Edu3)	7 (14.6%)	10 (38.5%)	
Country of birth			<**0.0001**
Mexico	48 (100%)	15 (57.7%)	
Central America		8 (30.8%)	
South America		3 (11.5%)	
Occupation			**N/A**
Farmworker	48 (100)		
construction		7 (26.9%)	
Production		6 (23.1%)	
Food preparation/restaurant		3 (11.5%)	
Maintenance/cleaning		3 (11.5%)	
Sales		1 (3.8%)	
Mechanic		2 (7.7%)	
Other		1 (3.8%)	
Unemployed		3 (11.5%)	
Pack years smoked at baseline, yrs	1.6695 ± 4.64	0.6501 ± 2.94	**0.3617**
Smoking status	18 smokers (37.5%)	2 smokers (7.7%)	<**0.0001**